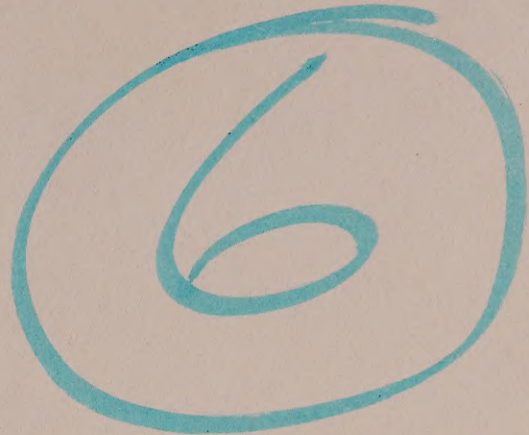


CA20N
Z 1
-83H021



Ontario



**ROYAL COMMISSION OF INQUIRY INTO CERTAIN
DEATHS AT THE HOSPITAL FOR SICK CHILDREN AND
RELATED MATTERS.**

Hearing held in Court Room 20
Court House
361 University Avenue
Toronto, Ontario

The Honourable Mr. Justice S.G.M. Grange

Commissioner

P.S.A. Lamek, Q.C.

Counsel

E.A. Cronk

Associate Counsel

Thomas Millar

Administrator

Transcript of evidence
for

June 30th, 1983

OFFICIAL COURT REPORTERS

Angus, Stonehouse & Co. Ltd.,
14 Carlton Street, 7th Floor,
Toronto, Ontario M5B 1J2

595-1065



ROYAL COMMISSION OF INQUIRY INTO CERTAIN
DEATHS AT THE HOSPITAL FOR SICK CHILDREN
AND RELATED MATTERS.

Hearing held in Court Room 20,
Court House, 361 University
Avenue, Toronto, Ontario, on
Thursday the 30th day of June,
1983.

- - - -

THE HONOURABLE MR. JUSTICE S.G.M. GRANGE - Commissioner
THOMAS MILLAR - Administrator
MURRAY R. ELLIOTT - Registrar

- - - -

APPEARANCES:

P.S.A. LAMEK, Q.C.)	Commission Counsel
E.A. CRONK)	
T.C. MARSHALL, Q.C.)	Counsel for the Attorney-
D. HUNT)	General and Solicitor
L. CECCHETTO)	General of Ontario (Crown
	Attorneys and Coroner's Office)
I.J. ROLAND)	Counsel for The Hospital for
R. DEVINS)	Sick Children
D. YOUNG	Counsel for The Metropolitan
	Toronto Police
W.N. ORTVED	Counsel for numerous Doctors
	at The Hospital for Sick
	Children
B. SYMES	Counsel for the Registered
	Nurses' Association of Ontario
	and 35 Registered Nurses at
	The Hospital for Sick Children



INDEX OF WITNESSES

<u>NAME</u>	<u>Page No.</u>
<u>ELLIS</u> , Graham (Dr.) Sworn	800
Direct Examination by Ms. Cronk	800

INDEX OF EXHIBITS

<u>No.</u>	<u>Description</u>	<u>Page No.</u>
13	Curriculum Vitae of Dr. Graham Ellis.	800
14	Digoxin Antiserum, publication by Antibodies Incorporated dated April, 1974.	831
15	(Reserved) - Three requisition forms: Form in use during period July 1980 to March 1981; form introduced with the Therapeutic Drug Monitoring Program; and the form currently used by the program.	903

Digitized by the Internet Archive
in 2023 with funding from
University of Toronto



A/BB/ak

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25

---Upon commencing at 10:00 a.m.

THE COMMISSIONER: Yes, Mr. Lamek.

MR. LAMEK: Mr. Commissioner, a housekeeping matter if I may. We have recently obtained and have now prepared bound sets of the exhibits from the Preliminary Inquiry in the Nelles matter. We've prepared copies for those counsel who are being funded on the same basis as transcripts of the evidence from the Preliminary were prepared and supplied and, that is to say, certain counsel will be sharing those things as others with a like interest. Those copies will be available for collection from the Commission's office on Monday. They amount to three stout volumes of documents.

Obviously not included are medical records and we propose to file those as separate exhibits in the very near future.

Copies are also prepared for those unfunded counsel who do not already have them, and I suppose there may be a modest or immodest charge for the preparation of the binders for those people, but they certainly will be available on Monday as well.

THE COMMISSIONER: As long as you don't make up the loss on the funded counsel, they



1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25

won't mind.

MR. LAMEK: That's right. They will all be available for collection at the Commission's office on Monday, Mr. Commissioner.

THE COMMISSIONER: Yes, all right, thank you.

MR. LAMEK: Mr. Commissioner, the next witness is Dr. Ellis, and I would ask you please ^{to allow} through Ms. Cronk to lead the evidence of Dr. Ellis.

THE COMMISSIONER: Yes, certainly.

Ms. Cronk, just a moment. Mr. Ortved is not here?

MR. YOUNG: Not as yet.

THE COMMISSIONER: No. Well, I will say it, the matter is not yet resolved and I may have something - well, I may have something next week. Yes, Ms. Cronk.

MS. CRONK: Mr. Commissioner, an additional housekeeping item if I may before I call Dr. Ellis to the stand.

We have now received and reviewed written comments or objections from a number of counsel concerning a number of the facts contained in the Statement of Prima Facie facts.



1
2
3 Most recently we received a set of
4 written comments from one particular counsel yester-
5 day and received another late in the afternoon on
6 Tuesday. Because of the timing of those deliveries,
7 and also because of the contents of the various
8 comments, Commission Counsel have prepared what is
9 styled as an addendum to the Statement of Prima
10 Facie facts. The purpose of that document is to
11 record for all counsel the paragraphs, if you will,
12 in the Statement of Prima Facie facts that now
13 appear to have been put in issue by various counsel
14 and, as well, where specific references have been
15 provided to Commission Counsel by other counsel
16 concerning other information or substitutional
17 facts that they feel should be in the Statement,
18 where that kind of reference to the public record
19 as it now exists has been provided, the Addendum
20 includes suggested changes, amendments or clarifica-
21 tion items to the Statement of Prima Facie facts.

19 That Addendum will be made available
20 for all counsel we hope by the conclusion of today
21 and, if not today, certainly by Monday morning for
22 their review. It would be our hope that we would
23 have further to say though about the Statement of
24 Facts and about the Addendum later next week.
25



1
2
3 I should add as well that all counsel
4 now have a copy as of this morning of the comments
5 received by Commission Counsel from all other counsel
6 so that they have those two types of documents to
7 review should they feel it appropriate to do so
8 before we deal with the matter for the next week.

9 THE COMMISSIONER: Yes, all right.

10 MS. CRONK: Thank you.

11 THE COMMISSIONER: Well then, I
12 take it then either today or Monday they will have
13 this Addendum and then at some time convenient next
14 week we'll discuss it. Is that correct?

15 MS. CRONK: That's correct, sir.

16 THE COMMISSIONER: Thank you.

17 MS. CRONK: The next witness,
18 Mr. Commissioner, is Dr. Graham Ellis from the
19 Hospital for Sick Children. Dr. Ellis, like others
20 that have already been called as witnesses and
21 others who will be called as witnesses has a number
22 of matters in respect of which he will giving
23 testimony at these hearing.

24 It is the intention this morning that
25 Dr. Ellis will give evidence concerning the
methodology existent in the Hospital during the
period July, 1980 to March of 1981 for the conducting



1
2 of assay tests on digoxin and, as well, to certain
3 of the techniques available today for that purpose.

4 He will be recalled as a witness
5 by Commission Counsel at a subsequent date, to talk
6 about specific tests that he conducted or that were
7 conducted under his supervision with respect to a
8 number of the children with which the Commission
9 is concerned.

10 So, the purpose again today is merely
11 methodology and general terms.

12 I would call Dr. Ellis.

13 THE COMMISSIONER: Fine, thank you.

14 DR. GRAHAM ELLIS, Sworn

15 DIRECT EXAMINATION BY MS. CRONK:

16 Q. Dr. Ellis, you previously
17 provided to me through your counsel a copy of your
18 Curriculum Vitae. I would like to show you a copy
19 now. Copies have been made available to other
20 counsel as well.

21 THE COMMISSIONER: Yes, what number
22 are we at, Exhibit 13.

23 ---EXHIBIT NO. 13: Curriculum Vitae of Dr. Graham
24 Ellis.

25 MS. CRONK: Thank you,
Mr. Commissioner.



1

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

Q. Dr. Ellis, as I understand it, you are at the present time an Assistant Biochemist in the Department of Biochemistry at The Hospital for Sick Children?

A. Yes.

Q. And you have held that position since November of 1976 to the present?

A. Yes.

Q. You were born, sir, in Derbyshire, England in October of 1945, is that correct?

A. That's correct.

Q. And dealing just with the highlights, if I may, of your rather lengthy Curriculum Vitae, you received a Bachelor of Science, an Honours Degree in Biochemistry from the University of Manchester, Institute of Science and Technology in England in 1967?

A. That's correct.

Q. And from August of 1967 to November of 1972, as I understand it, you worked as a Biochemist at United Sheffield Hospital in Sheffield, England.

A. Yes.

Q. From December of 1972 to



1

2

October of 1976 you worked as a Biochemist at the
Central Birmingham Health District, General
Hospital, Birmingham, England.

4

5

A. Correct.

6

Q. And in 1973 you obtained a
PhD from the University of Sheffield, England.

7

8

A. Yes.

9

Q. Was that in Biochemistry,
Dr. Ellis?

10

A. In Clinical Biochemistry, yes.

11

Q. And I take it that you
obtained that, or at least completed it while
working at the General Hospital in Birmingham?

13

14

A. Yes, I completed it there.

15

Q. In the fall of 1976 you moved
to Canada?

16

A. Yes.

17

Q. You obtained a position at
that time with the Hospital for Sick Children, as
I understand it?

19

20

A. Yes.

21

Q. Did you join the Hospital for
Sick Children at that time as an Assistant Biochemist?

22

23

A. I did, yes.

24

Q. And you have as well, as I

25



1

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

understand it, a cross appointment to the University of Toronto as an Assistant Professor in the Department of Clinical Biochemistry?

A. Yes.

Q. Is that an appointment you continue to hold today?

A. That is, yes.

Q. And you belong as well to a number of professional societies or organizations, Doctor. I don't propose to deal at length with those, they are fully set out in your Curriculum Vitae.

A. Yes.

Q. And, as well, you are the author or co-author of a number of professional publications in the area of clinical biochemistry, is that correct?

A. That's correct, yes.

Q. Could you briefly explain for us, Doctor, we have heard evidence in respect of this matter from other witnesses, but in your view, what is involved in the science of clinical biochemistry?

A. The science of clinical biochemistry is a science designed to study various



1
2 chemical constituents of blood, plasma and human
3 body fluids for the purpose of assisting physicians
4 in hospitals to come to a diagnosis.

5 Q. A diagnosis as to what, Doctor?

6 A. As to what might be wrong with
7 the patient in question.

8 Q. Okay. Now, I would ask you,
9 Dr. Ellis, if you would, to turn your mind to the
10 period of July, 1980 to March of 1981. As I under-
11 stand it, you were then an Assistant Biochemist,
12 as you are now, in the Biochemistry Department at
the Hospital, is that correct?

13 A. Yes, correct.

14 Q. What were your, in general
15 terms, responsibilities as an Assistant Biochemist
16 in the Department at that time?

17 A. At that time and also at present,
18 my responsibilities are for the radioimmunoassay
19 section. This section is concerned mainly with
20 the analyses of various hormones and doing tests
21 and, in addition, because digoxin is a radioimmuno-
22 assay, at the time that we were discussing, I was
responsible for that test at the Hospital for Sick
Children.

23 Q. All right. Now, I'll be coming
24
25



1
2 back to the test, the methodology of the test that
3 you conducted in a few moments, Doctor, but for
4 present purposes, to whom did you report at the
5 Hospital during that period of time?
6
7
8 -----
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25



B-1

1

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

A. My line of reporting was to Dr. J. G. Hill who is the Chief Head of the Department, of the Service Division of the Department of Clinical Biochemistry, of the Department of Biochemistry, and he reports to Dr. D. M. Goldberg.

Q. I am sorry.

A. Dr. Goldberg, who is the Head of the Department of Biochemistry at the Hospital for Sick Children.

Q. Now, in your position as Assistant Biochemist, and again during the period of time July 1980 to March of 1981 did you have others reporting to you, or were you responsible for the supervision of any others in that department?

A. Yes, I was responsible for the supervision of a number of technologists, I think there were probably about five at that time.

Q. Would those be the individuals that would actually conduct the tests.

A. They would, yes.

Q. Would you yourself on occasion conduct assays personally?

A. On some occasions, yes.

Q. During the period from July 1980 to March 1981 I take it there were specific facilities at the hospital available for the assays



B-2

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25

that you were responsible for, is that correct?

A. That is correct.

Q. Where were those facilities physically located in the hospital?

A. These were by and large physically located in the laboratory occupied in Room 3414, the lab where I work.

Q. That is on the third floor I take it of the hospital?

A. Yes, this is on the third floor.

Q. Is there more than one lab connected with the Biochemistry Department in the hospital?

A. Yes, there are several laboratories.

Q. During that period of time was there a main or general biochemistry lab?

A. Yes, there was.

Q. Is that the lab you just described to us as being where you worked?

A. No, this is more of a specialist lab looking at the radioimmunoassay aspect.

Q. Were radioimmunoassay tests conducted in the main biochemistry lab as well as



B-3.

1

2

the one in which you worked.

3

4

5

6

A. They were not conducted there,
no, but serum specimens, or blood samples may be
separated in the main laboratory and transferred to
our laboratory.

7

8

Q. And the assays themselves were
then conducted in your lab?

9

A. That is correct, yes.

10

11

12

13

14

Q. Now we have heard evidence
Dr. Ellis, from Mr. Cimbura of the Centre of Forensic
Sciences concerning the techniques for conducting
digoxin assays that were available to him at the
centre. Were you present last week in the courtroom
for the evidence of Mr. Cimbura?

15

A. Yes, I was.

16

17

18

Q. Can you tell me then, sir, what
method or methods were available to you at the
hospital during the period of July 1980 to March
1981 to conduct specifically digoxin assays?

19

A. We used radioimmunoassay.

20

21

22

Q. Were there any other methods
then used by the hospital for that purpose other
than the RIA?

23

A. No.

24

25

Q. Can you help us as well, sir,



B-4

1

2

3

4

with the purpose as you understand it to have been
for conducting digoxin assays in your lab at that
time?

5

6

7

8

9

A. Yes. Basically this was in-
patients who were being treated with digoxin to
establish the level of digoxin, the blood plasma
of those patients in order to assist the doctors
who were monitoring those patients who were being
treated.

10

11

12

13

14

15

16

Q. Would I correctly take it from
your answer Dr. Ellis, then, that the purpose of
the assays at that time would be to assist the
doctors with respect to their patients who were
receiving digoxin, was effectively to monitor the
appropriateness of the digoxin that had or had not
been prescribed for the patient involved?

17

18

19

20

21

A. At that particular time there was
no indication for measurement of digoxin in a
patient who had not been prescribed digoxin.

22

23

24

25

Q. So then the assays that you
would run would only involve patients who you knew
in the hospital to have been prescribed digoxin.

A. They had all been submitted
for analysis and that was the assumption that we
made.



B-5

1

2

3

Q. That they had in fact been
prescribed digoxin.

4

A. Sure.

5

6

7

8

9

Q. Was the purpose of running the
assay on those patients, as you understood it, to
assist the physician in the hospital in determining
the appropriateness of the dosage that had been
prescribed?

10

A. That is correct, yes.

11

12

13

14

Q. We have heard evidence as
well Dr. Ellis of a method described as the HPLC
method. During the period of time that we are
talking about I take it that technique was not used
in the hospital.

15

16

17

A. The technique of HPLC in
general is used in the hospital and there is
an instrument for HPLC in my laboratory.

18

19

20

21

Q. All right.

A. But it wasn't used for digoxin.

Q. At that period of time?

A. It still isn't used for

digoxin.

22

23

Q. Has it ever been used in the
hospital for digoxin assay?

24

A. No, not to my knowledge unless

25



B-6

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25

other departments are using HPLC for digoxin,
I don't know.

Q. Is there any particular reason
for that, Dr. Ellis?

A. Simply because the technique
is very lengthy and very involved. For most
clinical purposes radioimmunoassay is regarded as
the method of choice, by virtually all hospitals
that I know of, both in Europe and Canada and the
United States, radioimmunoassay is a method that
they would use for therapeutic drug monitoring of
digoxin, generally speaking.

Q. Would it be unusual then in
your view Doctor were a hospital for clinical
purposes to use the HPLC method for digoxin assays?

A. I would be very surprised if
there were any such hospitals using HPLC for the
measurement of digoxin on a regular basis.

Q. Do you know of any as we sit
here today in the Province of Ontario that would use
it?

A. No, I don't, no.

Q. Now with respect to the RIA
assay, that methodology that was in use. how long
has it been in use for digoxin assays in the hospital?

A. It has been in use since



B-7

1

2

January of 1975 I believe.

3

4

5

6

Q. I take it that the methodology itself as we have heard from other witnesses is capable of being used for assays on any number of drugs in addition to digoxin?

7

8

9

10

11

A. Yes.

Q. Prior to 1975 was it a technique that you were familiar with and that you had used in the hospital for other drug assays.

10

11

A. Well I didn't move to the hospital until 1976.

12

13

14

Q. I beg your pardon. To your knowledge was the RIA technique used in the hospital for the purposes of other drug assays prior to 1975?

15

16

17

18

19

20

21

22

A. Other drug assays I am not sure about. What I would say is that I came across a book the other day from an old book, which suggested that samples had been sent out to Mount Sinai Hospital in 1972. In relation to a kind of history of all of this I understand that in about 1974 Dr. Cherian and a number of other people were asked to implement the radioimmunoassay at the Hospital for Sick Children.

23

24

25

Q. Dr. Cherian was then with the Hospital for Sick Children?

A. Dr. Cherian, yes. C-H-E-R-I-A-N.



B-8

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25

Q. As far as you are aware
digoxin assays were commenced in this technique in
1975?

A. In 1975 I think the first
patient results were produced. That followed a
study in about 1974 I understand where they were
looking at various alternative methodologies for
the measurement of digoxin by radioimmunoassay.

Q. And that was the one that was
ultimately selected to be implemented and used on
a regular basis in the hospital?

A. That is correct, yes.

Q. Now Doctor we have heard from
a number of witnesses to date evidence concerning
the basic principle that is involved in the RIA
test, and that has been described variously as in
essence a competition between radio-active digoxin,
or digoxin labelled with radio-activity with a
patient sample which may or may not contain digoxin
for a binding site on an antibody that is used in
the process. Is that in your judgement a fair
description of the basic principle of how the test
works?

A. Yes I think that is a summary



B-9

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25

of the principles involved.

Q. Doctor I would like to review with you very briefly the actual methodology and steps involved in the test as it was used in your lab in the hospital during the period of July 1980 to March 1981. I would ask you for the moment to direct you mind simply to that time period.

As I understand it the first step involved in the process, if I can describe it as that, and I am going to try Doctor to put this down in a diagramatic way and you tell me if I did any of the steps wrong. As I understand it the first step, the first ingredient of the test involves the use of what are known as standards, is that correct?

A. Standards are required for the test, yes.

Q. Can you explain for us briefly what standards are?



C/DP/ak

1

2

A. What the standards are -

3

standards are solutions containing a known amount
4 of digoxin.

4

5

MR. BOGART: Excuse me - could you
6 just repeat that?

6

7

THE WITNESS: Standards are
7 solutions containing a known amount of digoxin.

8

9

MS. CRONK: Q. How many standards
9 were used by you, during this time period, to run an
10 RIA assay?

10

11

A. The number was five. With each
12 batch five standards would be run in order to
13 calibrate the procedure.

13

14

Q. I'm sorry, in order to
14 calibrate the procedure?

15

16

A. In order to calibrate the
16 procedure, yes.

17

18

Q. Is that the purpose for using
18 standards?

19

A. That is correct.

20

21

Q. How often would you have to
21 calibrate the equipment, using those standards, to do
22 an RIA assay?

22

23

A. With every single run of assays
23 you would run a set of standards.

24

25



1

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

C2

Q. I take it from what you are saying that the five separate standards that you obtained each contained a known amount of digoxin. Is that correct?

A. That is correct. We obtain a commercial material which, when reconstituted, is supposed to contain a particular stated amount of digoxin.

Q. And you obtain those commercially?

A. Yes.

Q. During this period of time, Doctor, where did you acquire - where did you purchase your supplies?

A. We obtain these from Corning Medical.

Q. Doctor, I am just going to list the standards if I may. I take it they are effectively in the form of test tubes containing a certain amount of known digoxin?

A. The standards are small bottles containing the substances described - the standards described.

Q. At the risk of not doing bottles correctly maybe I can just show it this way.

A. Yes. From that bottle you would



1
2 take a small quantity and you would then put it into
3 a test tube - two test tubes, in fact, because the
4 assay is usually done in duplicate.

5 Q. Could you help us, Doctor,
6 do you recall today what the concentrations of
7 digoxin were in each of the standards that were in
8 use that during that time period?

9 MR. MARSHALL: I don't want to
10 cause difficulty to Ms. Cronk --

11 MS. CRONK: Are you having difficulty
12 seeing it?

13 MR. MARSHALL: -- but could you make
14 it a little bigger.

15 MS. CRONK: I will try.

16 MR. MARSHALL: I know you are not
17 used to this.

18 THE COMMISSIONER: There may not
19 be enough room. I do not know what the intention is -
20 are you going to put them all on?

21 MS. CRONK: I am going to try. I
22 hope, Mr. Commissioner, that I understand the basics
23 of the principle, and if I am right I guarantee I will
24 get them on the page. How large, Mr. Marshall, I do
25 not know, but we will see how we do.

Q. Do you recall today, Dr. Ellis,



C4 1
2 I take it that each of the standards have a specific
3 concentration of digoxin and each standard was
4 different.

5 A. Yes.

6 Q. Do you recall today what
7 concentrationsof digoxin were available in the
8 standards that you purchased and used.

9 A. The values stated by Corning
10 Medical were 0, 0.5, 1.0, 2.5 and 5.0 nanograms
11 per ml.

12 Q. I am sorry, 1.0, 2.5 - what
13 was the fourth one?

14 A. I think I said 0, 0.5, 1.0,
15 2.5 and 5.0 nanograms per ml.

16 Q. Now, when you obtained the
17 standards did you actually measure the standards
18 to confirm the amount of digoxin in each or was that
19 information provided to you directly by the supplier?

20 A. That information was provided
21 to us directly by the supplier.

22 Q. In addition to the standards,
23 as I understand it, you used as well, or you used at
24 the time, a number of control samples. Is that
25 correct?



1

2

A. That is correct.

3

Q. Can you briefly explain for us

4

what control samples were, in this context?

5

A. Basically a control sample is

6

a pool of human serum which has been prepared by

7

a commercial company and to that pool of human

8

serum various constituents have been added, including
digoxin.

9

Q. All right.

10

A. Quite often three levels are used.

11

There is a pool which has had relatively little

12

addition of digoxin; one that is at an intermediate

13

level and another that is very often at a sort of

14

toxicological borderline level.

15

THE COMMISSIONER: Those words you
are using, Doctor, is that "pool"?

16

THE WITNESS: Pool, yes.

17

THE COMMISSIONER: Pool, p-o-o-l, as

18

in swimming?

19

THE WITNESS: Yes, as in swimming,

20

yes. It is a term quite often used. If we were

21

to take blood from 10 members here and we were to

22

mix those bloods, that would be what we would call

23

a pool. It is just commonly used in a laboratory

24

situation.

25

C5



1

2

MS. CRONK: Q. And the digoxin, I

3

take it, along with another of other constituents

4

would be floating in the pool of each control

5

sample?

6

A. It would be added to the

7

pool and would dissolve in the control sample. The

8

manufacturers, having made a very large amount of

9

this material, would then transfer certain amounts

10

into specific small bottles. That material would

11

then be freeze-dried and then it would be distri-

12

buted, firstly, to companies who would have interest

13

in that material and, secondly, to laboratories who

14

were performing the analyses that that material

was designed to be the control for.

15

Q. Such as your own?

16

A. Such as our own.

17

Q. Now you said that you acquired
those commercially?

18

A. Yes.

19

Q. Were they acquired as well
from Corning Standards or from somewhere else?

20

21

A. No, I think at that particular
time they were attained from the Ortho Company.

22

23

Q. I am sorry --

24

A. The Ortho Company.

25



1

2

3

4

5

6

Q. When you receive the control samples, did your lab or someone in your lab add a known amount of digoxin to them or did they come in in a freeze-dried preparation, with a known amount already in them?

7

8

9

10

11

12

13

A. They came in in a freeze-dried preparation. All that was necessary was for us to open the vials, adding a known amount of water, perhaps 3 mls, perhaps 5, according to the instructions, and then that would be a reconstituted material, a similar composition, one would hope, to the patient samples that we were dealing with on a day to day basis.

14

15

16

Q. At that time I believe you indicated that it was usually three control samples that were used?

17

18

19

20

21

22

23

24

25

A. Yes.

Q. Was that the case in your lab?

A. Yes.

Q. Were those three control samples used variously for any number of digoxin assays or were different control samples used for each assay?

A. Having reconstituted the material by adding water and allowing the freeze-



1
2 dried material to dissolve, it would be our practice
3 to split the material into various aliquots,
4 little small quantities, freeze those small
5 quantities in small tubes, and then each day we
6 would take out a fresh sample.

7 Q. So a fresh particular sample
8 would be used for each assay?

9 A. That is correct.

10 Q. Can you help us today, Doctor,
11 as to what the concentrations were in the three
12 control samples that you purchased for the purpose
13 of running any individual digoxin assay?

14 A. At the time that the --

15 Q. At the time of July 1980 to
16 March of 1981.

17 A. There were basically three
18 levels produced by the Ortho Company. The claimed
19 value for the first one was 1.0 nanograms per ml;
20 the claimed value for the second one was 2.0 and the
21 claimed value for the third one was 2.8.

22 Q. And those as well were measured
23 in nanograms per ml?

24 A. Nanograms per ml.

25 THE COMMISSIONER: I did not get
that word again, that phrase. What is it that you



1
2 said, before the figures?

3 THE WITNESS: The claimed value.

4 THE COMMISSIONER: The claimed value,
5 that is the value of the digoxin, I take it?

6 THE WITNESS: Yes, the value of
7 digoxin that the manufacturer claims is in that
8 particular sample of serum that he has prepared.

9 MS. CRONK: Q. By claimed value,
10 Dr. Ellis, if I could just make sure that I under-
11 stand that, you are referring to the information
12 provided by the supplier as to the concentration of
digoxin in the sample?

13 A. That is right. This is the
14 inference - this is the claimed value we would use
15 in our hospital, based on the information that the
16 supplier supplied us with.

17 Q. The next ingredient, as I under-
18 stand it, Dr. Ellis, is what we have all heard
about, the radioactive digoxin.

19 Can you tell me, first, where you
20 obtained, again during this period of time, the radio-
21 active digoxin that you used for your assays?

22

23

24

25



D/BB/ko

1

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

A. This was obtained from the
New England Nuclear Company.

Q. And, as I understand it, that
sample or ingredient, if you will, was essentially
digoxin that had been treated with radioactivity?

A. This is a derivative of
digoxin which has been treated, to which iodine,
radioactive iodine has been incorporated in the
molecule. It is not strictly speaking digoxin.

Q. And that radioactive sample -
well, let's back up a moment. As I understand it,
the iodine element is added to digoxin, thus
introducing a radioactive element into a known amount
of digoxin, is that correct?

A. Not really, no.

Q. All right.

A. If we consider let's say the
thyroid hormone.

Q. Yes?

A. Thyroxine, then this contains
iodine already.

Q. Yes?

A. And it is floating around in
your blood and in mine. So, all that is necessary to
make that radioactive is to incorporate radioactive



1

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

D 2

iodine into that molecule. The molecule of radio-
active iodine is exactly the same - the molecule
labelled with the radioactivity is identical to the
physiological molecule.

Q. All right.

A. Now, the structure of digoxin
is such that there is no iodine in the drug digoxin.
So, it is necessary to modify the digoxin in such a
way that an iodine molecule can be incorporated into
the label of material.

Q. And the end complex, or the
end molecular product, as I understand it, is a
combination of both the iodine component, the radio-
active component and digoxin?

A. Yes.

Q. All right.

A. Plus possibly some other ring
structure such as tyrosine or histidine.

Q. All right.

A. So, it is not strictly digoxin
but it is similar to it in many respects.

Q. All right, thank you. And you
have told me that you obtained that commercially, as
I understand it, from New England Nuclear?

A. That's correct.



D 3

1

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

Q. All right. When you obtained that from a supplier, did that come in in known quantities? Did you know how much of the radioactive compound that you had that you were going to use for your assay?

A. It did come in in known quantities, yes.

Q. All right. Now, perhaps we could just add that, Doctor.

I will come back in a moment, Doctor, to the reason for the particular shape that I have drawn there. It is rather curious looking at the moment; it will get worse I assure you!

Can you tell me this, Doctor. In respect of the standards and the control samples that you use in your assay, is any radioactive or iodine treated compound added to either of those?

A. No.

Q. All right. Now, the next --

A. Not at that particular stage, no.

Q. All right.

A. The final mixture is made which incorporates the radioactively labelled digoxin, but there is no radioactive iodine label in the standards



D 4

1

2

or the controls as they are purchased from these
various companies.

3

4

Q. When you receive them?

5

A. That's correct.

6

7

8

9

Q. Now, but prior to running your
assay, do you add to the standards that you've
obtained commercially and to the control samples
that you have obtained commercially any amount of the
radioactive compound?

10

A. You do, yes.

11

Q. All right.

12

A. A fixed, a constant amount.

13

Q. And by that you mean the same
amount is added to each standard?

14

A. Correct.

15

16

Q. All right. And the same amount
is added to each control sample?

17

18

19

20

A. Yes. A particular volume of
the control sample is transferred to a second tube
and in that second tube radioactive digoxin is added
to that.

21

Q. All right. And it is the same
volume or the same amount in each of the tubes?

22

23

A. That's correct.

24

25

Q. Now, the next component, if I



1

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

D 5

can describe it that way, of the assay, as I understand it, is obviously the patient's sample that you obtained internal to the hospital. It's been sent to you with the assay?

A. Yes.

Q. And that is, I believe, what will be called the sample of interest?

A. Okay.

Q. Is that right?

THE COMMISSIONER: The sample of ...?

MS. CRONK: Interest.

THE COMMISSIONER: Interest?

MS. CRONK: That's the sample in respect of which the assay is being conducted, is that correct, Doctor?

THE WITNESS: That's correct, yes.

MS. CRONK: Q. And that sample, as I understand it again, in the period, July of 1980 to March of 1981, would it be fair to say you expected to contain some amount of digoxin?

A. That's correct.

Q. And those samples came from individual patients within the hospital and were forwarded to your lab for testing, is that correct?

A. That's correct.



1

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

Q. But at the beginning of the assay, you didn't know, am I right, the amount of digoxin in the patient's sample because if you did there would be very little purpose in running the assay?

A. Correct.

Q. All right. And the next component, Dr. Ellis, of the test - it's getting worse, isn't it - the next component of the test, as I understand it, is the antibody that is the essential ingredient to the RIA assay, is that correct?

A. Well, all constituents are essential.

Q. All right.

A. You can't do a radioimmunoassay without an antibody.

Q. Thank you. Where did the hospital during this period of time obtain the antibodies that it used in the RIA assays that you conducted?

A. These were obtained from Antibodies Incorporated, California.

Q. Did the particular antibody that you obtained from that company in California have any particular affinity that you are aware of



1

2

for drugs other than digoxin?

3

A. Yes, it had an affinity for
digitoxin.

4

5

Q. Digitoxin?

6

A. Yes.

7

Q. Any others?

8

A. Dealing with a handout that

9

the company provided in April of 1974, cross-
reactions with progesterone, which is a hormone

10

present in plasma, testosterone, estradiol,

11

cholesterol and corticosterone are all much less

12

than 0.1 percent. In other words, there is negligible

13

cross-reaction with these various substances that were

14

tested with that antiserum at that time by that
method.

15

Q. Are you referring to a handout

16

that was provided to you by the supplier of the anti-

17

bodies, Dr. Ellis?

18

A. Yes, I have obtained this

19

actually from Dr. Cherian last week when you expressed
interest in this.

20

Q. Would you have a copy available

21

that we could mark as an exhibit and perhaps at the

22

break we could make copies for other Counsel?

23

A. By all means, yes. I might

24

25



1

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

point out, I think there is an error on this which says digoxin cross-reaction is only 1 percent. I believe that that should say digitoxin.

THE COMMISSIONER: What's it called, Ms. Cronk, what's the title?

MS. CRONK: It's Digoxin Antiserum, publication by Antibodies Incorporated dated April, 1974.

THE WITNESS: Excuse me, could I give you this copy, please, I have written on the other one.

MS. CRONK: All right.

THE WITNESS: Thank you.

THE COMMISSIONER: Exhibit 14.

--- EXHIBIT NO. 14: Digoxin Antiserum, publication by Antibodies Incorporated dated April, 1974.

MS. CRONK: Q. Thank you, Dr. Ellis. I will return to the cross-reactive in a few moments if I may.

Now, dealing with the antibodies, as I understand it, in the assay itself there are any number of antibodies that are actually used and involved in the assay, is that correct?

A. I am sorry, can you say that again?



1

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

Q. There are any number of anti-bodies in terms of the number of molecules that are involved. There is more than one that are used in the assay?

A. You mean in our particular assay?

Q. Yes.

A. The antibody that we obtain is I think from one or perhaps several rabbits. Those antibody molecules will be slightly different in character. It will be a mixture essentially of anti-bodies.

Q. And there are a number of those molecules that are at work in the assay, it's not just one?

A. Oh yes, correct, yes.

Q. Well, for the purposes of this illustration, Dr. Ellis, I would like to just draw one if I may. But tell me if this is a fair statement. As I understand it, the competition that we've heard about between the radioactive digoxin and the patient sample digoxin for binding sites on the antibody used in the assay effectively works like a locking mechanism in the sense that the radioactive digoxin molecule and the patient digoxin sample molecule have features which



1

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

all them in the same way to bind on the antibody and it is really a first come first serve kind of principle. Is that a fair statement of the principle?

A. Yes, there is competition between similar molecules. Well, the same molecule - I'm sorry, similar molecules for the antibody.

Q. Now, if we use that kind of a figure as the illustration of the antibody, Doctor, and you can tell all of us are becoming educated to this process, as I understand it, the insert on the antibody would effectively be, in this example, the binding site?

A. Yes, it would be a specific binding site.

Q. All right. And what I have shown as effectively appendages on the radioactive digoxin and an appendage on the patient sample of digoxin, is that part of the molecule which would allow it to lock in to a binding site on the antibody; is that correct?

A. This is the principle, yes.

Q. All right.

A. Yes.

Q. And as I understand it, there is an equilibrium that's created in that locking in



1
2 or binding process, Doctor, am I correct in that, so
3 that in fact if we were to show in a diagramatic way
4 the binding process, it would look something like
5 this; is that correct?

6 A. Yes.

7 Q. You're hesitating, Doctor,
8 why is that, aside from the fact that I admit no
9 artistry in this?

10 A. Okay, the primary assumption
11 is that the antibody molecule will bind one molecule
12 of digoxin. Now, I'm not quite sure from your
13 illustration whether you have - does that indicate
14 this?

15 Q. All right. Well, let's be
16 very clear about that. That's what I meant about the
17 first come first serve kind of concept. Would you
18 link this to three molecules effectively interreacting
19 amongst one another, only one molecule is going to
20 bind on that particular antibody?

21 A. That's right.

22 Q. It is either going to be the
23 radioactive digoxin component or it's going to be the
24 patient's sample of digoxin. It's going to be one or
25 the other or both?

A. It's going to be the digoxin



1

2

from the patient sample you mean?

3

Q. That's right.

4

A. Right.

5

Q. It's going to be either that

6

or the radioactive component. Only one of them can
bind on that particular site on that antibody?

7

A. At that particular moment,

8

yes.

9

Q. Okay, right. Now, as I under-

10

stand it, in the assay which you conducted in the

11

hospital there is yet another step and that is after

12

the binding has taken place on the antibody, it is

13

necessary to determine how much radioactive digoxin

14

has in fact become bound to the antibody. Is that

15

correct?

A. Yes.

16

Q. All right. And how do you go

17

about determining that?

18

A. Well, basically some of the

19

radioactive material is bound to the antibody, some

20

is in free solution. So, you have to use some kind

21

of a separation technique in order to separate these

22

two components. The way that we use at the Hospital

23

for Sick Children at that particular time, and it

24

still is to add charcoal and that charcoal will take

25



1
2 up, will absorb the free digoxin and it will
3 essentially leave behind the antibody found in
4 digoxin.

5 Q. All right.

6 A. Having mixed the mixture at
7 the end of the equilibrium with charcoal, you can
8 then centrifuge the sample, spin it down in the
9 centrifuge and the weight of the charcoal will cause
10 it to go to the bottom of the assay tube, taking
11 along with it the free digoxin and leaving behind
12 in a solution the antibody bound digoxin.

13 Q. Can we take that, Doctor,
14 step by step?

15 A. Yes.

16 Q. So that I at least feel I
17 understand what you're saying.

18 As I understand it, the first step
19 is that the inter-reaction amongst these three
20 molecules results in either radioactive digoxin or
21 the patient sample digoxin becoming bound to the
22 antibody?

23 A. Yes.

24 Q. Right. But at that stage, you
25 don't know which is bound to the antibody, whether
it's the radioactive treated digoxin or the patient



1

2

sample containing digoxin. Am I correct in that?

3

A. Yes.

4

5

6

7

8

9

10

Q. All right. Nor do you know, because we must remember that there is more than one antibody at work here and more than one molecule of radioactive digoxin and more than one molecule of the patient sample, nor do you know the total amount of radioactive digoxin that has become bound up in the process and the total amount that is free or unbound. At this stage you don't know that?

11

12

13

14

A. That's right. You have a solution to which you add the radioactive material and you have no way of deciding where that radioactive material is.

15

16

17

18

19

Q. All right.

A. Until you try to separate the bound and the free variety of radioactive material.

Q. And the separating agent that you then use in your assay, as I understood it, is charcoal?

20

21

22

23

24

25

A. Yes.

- - - -



/DM/ak

1

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

Q. If I have understood correctly what you said the effect of the addition of charcoal to the solution was such that the amount of bound digoxin would rise to the surface, and the amount of unbound digoxin would attach itself to the charcoal at the bottom of the solution, is that correct?

A. You would add charcoal to the solution.

Q. Yes.

A. And the unbound digoxin would attach itself to the charcoal, it would become absorbed on the charcoal.

Q. Yes.

A. The charcoal particles are kind of suspended in solution because they are fairly small, and so there is a process which takes place over about 10 minutes that we leave the sample with the charcoal suspension in place. We then centrifuge the sample.

Q. Yes.

A. Spin it out at high gravity and effectively under these high gravity conditions the heavy material, the charcoal is centrifuged to the bottom of the tube.



1

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

Q. And that contains what effectively was the unbound or free floating digoxin because it has been absorbed in the charcoal?

A. Yes.

Q. And the bound digoxin is at the top of that solution with the charcoal at the bottom?

A. It is not strictly at the top, it is in the solution with a small pellet of charcoal at the bottom.

Q. And has not been absorbed by the charcoal?

A. That is correct, it is not floating, that is correct.

Q. But it is the fluid, it hasn't been absorbed by the charcoal?

A. Right.

Q. And I take it then that you then remove either the bound digoxin from the sample that you have now centrifuged?

A. Yes, you pour off the fluid material from the charcoal pellet and the fluid material contains the antibody bound material.

Q. Dealing just with the charcoal itself for a moment, Doctor, was that as well



1
2 purchased commercially by the hospital during the
3 period of time we are talking about?

4 A. Yes, it was.

5 Q. And where it was purchased
6 from?

7 A. British Drug House Company.

8 THE COMMISSIONER: I'm sorry.

9 MS. CRONK: Q. I'm sorry, would
10 you say that again?

11 A. B.D.H., British Drug House..

12 THE COMMISSIONER: You purchased
13 what from them?

14 THE WITNESS: The charcoal.

15 THE COMMISSIONER: Obviously it is
16 some special kind of charcoal?

17 THE WITNESS: It is actually called
18 activated charcoal, but it is very similar to the
19 kind of charcoal that you might obtain for the
20 barbeque, but it is very, very fine, it is relatively
21 chemically clean.

22 THE COMMISSIONER: What was that?

23 THE WITNESS: Chemically clean.

24 MS. CRONK: Q. It is not the kind
25 of charcoal that some of us might buy for our patio
facilities, it is specially treated for purposes of



E4

1

2

being used in this assay?

3

4

A. It is, yes. The material for
your barbeque may work.

5

6

Q. But you wouldn't want to use it?

7

8

9

10

11

A. I would prefer not to.

Q. Doctor, as I understand it
where we are now in the process is that you now know
the amount of bound digoxin, that is the amount
of that element that has attached itself or bound
itself to the antibody and you have accomplished
that.

12

13

14

THE COMMISSIONER: I'm sorry, you
may know, I thought it is the unbound digoxin that
attaches to the charcoal?

15

16

17

THE WITNESS: That is correct.

18

19

20

21

22

THE WITNESS: It is a process of
subtraction. Essentially by decounting the upper
layer after the spinning down of the charcoal to the
bottom of the tube, by decounting the upper layer into
a second tube, a third tube if you will.

23

24

25

THE COMMISSIONER: Yes, all right.

MS. CRONK: I perhaps may have



1

2

been a little misleading then, Mr. Commissioner, and
I apologize for that.

3

4

Q. Tell me this, Dr. Ellis, the
amount of the digoxin that has not attached itself
to the charcoal is the bound digoxin?

5

6

7

A. That is correct.

7

8

Q. Is the separation of those
two after the use of the charcoal physically
accomplished simply by pouring the fluid out?

9

10

A. That is correct.

11

Q. Of the bound digoxin?

12

A. Yes.

13

Q. And what you are left with in
the tube, or the one apparatus, is the charcoal with
the unbound digoxin and you have now poured out the
bound digoxin?

14

15

16

A. Yes.

17

Q. Is that bound digoxin purely
digoxin from the patient sample, or does it also
include some element of the radioactive digoxin?

18

19

20

A. It contains some element of
the radioactive digoxin.

21

22

Q. And at this stage you still
don't know what the volume or the amount is of the
radioactive digoxin as compared to the patient

23

24

25

E5



1

2

sample digoxin, is that right?

3

A. I think the sentiment of what

4

you say is correct, yes.

5

Q. The sentiment, right. Do you,

6

when you have poured off the amount of bound digoxin,

7

know what proportion of that element is radioactive

8

digoxin as opposed to digoxin from the patient

9

sample?

10

A. Not simply after you have

poured it out, but you then transfer it to a machine

11

which measures the radioactivity.

12

Q. What is that machine called?

13

A. It is called a Gamma Counter,

14

G-a-m-m-a.

15

Q. What is its purpose?

16

A. Its purpose is to measure

radioactivity.

17

Q. And what is the end result

18

that you get off that machine, do you physically

19

get a reading of some kind, do you get a printout,

20

what do you get?

21

A. You get a reading, a printout.

22

Q. And what does that printout

tell you?

23

A. That printout tells you the

24

25



1
2 amount of radioactivity in the tube that you put
3 into the machine.

4 Q. You now know, Dr. Ellis, then
5 the amount of radioactive digoxin that has been
6 poured out and that is the amount that effectively
7 became bound to the antibody, is that correct?

8 A. Yes.

9 Q. How do you then move from that
10 piece of information to knowing how much patient
11 digoxin was present in the sample that you assayed?

12 A. Well, basically you do this
13 whole process for the standard tubes, for the control
14 tubes and for the patient tubes. So you end up
15 with a particular radioactive count for standards,
16 and the controls, and the patients. You then examine
17 the counts in the standard tubes and with the
18 assistance of the computer you can draw a kind of
19 curve which relates the amount of reactivity measured
20 to the amount of non-labelled digoxin that was
21 present in the standards.

22 Q. Let me make sure I understand
23 that part of it. Have you, from the beginning of
24 the assay, run the control samples through the assay
25 along with the patient sample?

A. Yes, along with the standard



1

2

samples.

3

Q. And along with the standard

4

samples?

5

A. Yes.

6

Q. So once you get to the point

7

where you have a readout on a particular assay as

8

to the amount of radioactive digoxin that you have,

9

do you then compare that amount to the amount that

10

you know was in the standards because it was

11

physically put into the standards before the assay

12

was commenced?

A. I'm not clear that I understand.

13

Q. All right, that's fair. Perhaps

14

it is best to ask you this; what relationship is

15

there, what purpose do the standards serve once you

16

have a readout from the Gamma Counter as the amount

17

of radioactive dig in the particular sample that

18

you are assaying?

A. You can essentially draw a

19

calibration graph, either manually or using a

20

computer which relates the concentration of those

21

standards to the final radioactive count obtained

22

for the individual tubes.

Q. And you told us we have five

23

standards that work?

24

25



1

2

A. Yes.

3

4

Q. If one were to do this in a plotting fashion, not on a computer, Dr. Ellis.

5

A. Yes.

6

7

8

9

Q. I don't mean a plodding, I mean a plotting fashion, as I take it the first part of the chart, or the curve, would be the amount of your standards, the amount of known radioactive digoxin, is that correct?

10

A. Yes.

11

Q. And you have five of those?

12

A. Yes.

13

14

Q. And you also know the amount of radioactive digoxin that has come off the Gamma Counter reading?

15

A. Yes.

16

17

Q. And you plot that as well?

A. That is correct.

18

19

20

Q. And those are various levels of radioactive digoxin that you know are in the standards as well?

21

A. Correct. I'm sorry, those various amounts of what?

22

23

24

25

Q. That you know are in the standards, you know how much radioactive digoxin



1

2

has been put in the standards?

3

A. Well you have, yes, you have,
4 but not in the sense that you imply it.

5

Q. All right. I'm sorry.

6

A. Because your standard contains
7 unlabelled digoxin as it comes from the manufacturer.

7

Q. Yes.

8

9

A. So what we actually plot is
10 the amount of unlabelled digoxin that the manufacturer
tells us he has put in.

11

Q. Yes.

12

A. And then we plot the radio-
13 activity alongside that.

14

Q. In other words, and you told
15 me earlier that you add to the standards that you
16 have obtained from the supply a known amount of
the iodine treated compound?

17

A. Yes, we add to the assay
18 mixture.

19

Q. So am I right that on the
20 particular sample on which you conducted the assay
21 you got a specific readout as to the amount of radio-
22 active digoxin that has come off the Gamma Counter,
is that correct?

23

A. Yes.

24

25



1
2 Q. And you can plot that against
3 the amount that you know to have been in the standards
4 because you added it to the standards. So the
5 results, and you stop me if I am wrong, the result
6 would be that you can plot on a curve where the
7 amount of radioactive digoxin in the patient
8 sample should fall according to the standards?
9 I am obviously explaining that badly, is there a
10 better way to do it? Would you explain again the
11 relationship between how you use the standards to
12 determine the amount of patient digoxin in the
sample you have assayed?

13 A. Yes. On the bottom axis of
14 your graph you should plot something like 0.5, 1.0,
15 2.5 and 5. This represents in the standards the
16 amount of unlabelled digoxin present and the
17 concentration of that material in the standards as
18 used. On the other axis you should plot the
19 counts finally obtained from the Gamma Counter,
from the tubes that were used for the standards.

20 Q. That could be anything
21 depending on the amount of radioactive digoxin that
22 was bound up.

23 A. It could, it would probably be
24 of the order of say three and a half thousand at
25



1
2 the start and it would probably go down to 1,000 or
3 so on the final standard, and there would be a
4 gradation as you draw on the graph.

5 Q. And as a result of that
6 process whether you do it manually, or whether you
7 accomplish it by computer, do you then know the
8 amount of patient digoxin that was contained in the
9 patient sample?

10 A. Well, you know from this how
11 the standards behave, okay. If you can perhaps
12 maybe draw on your little graph some number like
13 $3\frac{1}{2}$ thousand right at the top, would you mind doing
14 that, and about a thousand somewhere at the bottom.

15 Q. Up here?

16 A. Yes, sure.

17 Q. $1\frac{1}{2}$.

18 A. And 1,000 at the bottom some-
19 where. If you then have treated a patient sample,
20 or a control sample in an identical manner to the
21 way you treated the standards, you can then come
22 to this graph and if you get an answer like $3\frac{1}{2}$
23 thousand, looking at this graph you can say that
24 there is virtually zero digoxin in the patient's
25 sample.

Looking at this graph, supposing a



1
2 second patient had had a level like 1,000, you
3 could then say that because the standards that had
4 a level of let's say 2.5, or let's 5, had 1,000
5 counts in their tubes that the patient must have
6 had a level of 2.5 or 5.

7 Q. In other words, the standards
8 will tell you how much the radioactivity digoxin
9 as compared to patient digoxin it contained in
10 the particular sample on which you run the assay,
11 and that is because you know where the radioactive
dig in the standard is to be plotted on this graph.

12 A. I don't think I said anything
13 about radioactive digoxin in the patient sample.

14 Q. No, I am sorry. At the end
15 of your assay?

16 A. Right.

17 Q. At the end of the assay, one
18 more time, you will know how much patient digoxin
19 is in the sample that you have assayed because you
20 know where according to the calibrations provided
21 by the standards the radioactive components should
22 fall on the graph.

23 A. Correct.

24 Q. You can relate those two?

25 A. Yes.



1

2

3

4

5

Q. Now, at the end of the assay
and again dealing with the period of July 1980 to
March 1981, did you express the amount of digoxin
in the patient sample in nanograms per millilitre?

6

A. We did, yes.

7

8

9

10

11

12

13

Q. The system that you have just
described to us, Dr. Ellis, and I apologize if I
have made it more confusing than it need have been,
but that certainly helped me to understand it, that
was effectively the step by step procedure that
applied in running an RIA assay in your laboratory
in the period July 1980 to March 1981, is that
correct?

14

A. Yes.

15

16

17

18

19

20

21

22

23

24

25



F-1

1

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

Q. Is that in principle the same process that you use today to run RIA assays in your lab?

A. Essentially the same, yes.

Q. Let us take it in terms of the component parts of it, dealing now with today, as you sit here.

A. Okay.

Q. Are the standards still purchased from the same company as they were in July of 1980 to March of 1981.

A. No, the standards are actually prepared by Dr. Soldin's laboratory. We ran into some difficulties with that particular supplier.

Q. Dr. Soldin holds what position in the hospital?

A. He is the Associate Biochemist and he is the Director of the Therapeutic Drug Monitoring Program.

Q. And he now produces the standards that you use to run the RIA assays?

A. Yes.

Q. When did he start to do that? When did you stop buying them commercially?

A. I think sometime last year.



F-2

1

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

Q. Are the antibodies that you use in RIA assays today purchased from the same source as they were in the time period we are talking about?

A. Yes.

Q. You still get them from Antibodies, Inc.? What about the radioactive digoxin?

A. That is still obtained from New England Nuclear.

Q. What about the charcoal?

A. That is still obtained from the same source.

Q. You don't make your own charcoal in the hospital?

A. We prepare a solution from the commercial supplier of powdered charcoal.

Q. What about the control samples. Do you still get those from the same source as you then did?

A. I think they are obtained from Hyland Diagnostics.

Q. Hyland?

A. Hyland. H-Y-L-A-N-D.

Q. Other than the RIA assays and



F-3

1

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

test methodology that is now used in the hospital for digoxin tests, is there any other technique that is presently being used by the hospital to run digoxin assays, Doctor?

A. Yes, the fluorescence polarization technique is being used.

Q. Is that technique used in your lab?

A. No.

Q. Do you personally have any experience with the use of that technique?

A. Not hands-on, no.

Q. Who is using that methodology for digoxin assays?

A. Dr. Soldin is.

Q. So we should ask him about that?

A. Surely.

Q. How long, Dr. Ellis, both in the period of July 1980 to March of 1981, and today as you sit here, would it take for you in your lab to run an RIA assay from start to finish for digoxin?

A. We would start to gather together the samples at perhaps 10:30 or 11:00



F-4

1
2 o'clock in the morning. We would probably start
3 the assay at 11:15, maybe 11:30, and the results,
4 depending on the size of the batch, would probably
5 be ready by about 1:00 o'clock or 1:15 in the
6 afternoon, so approximately two and one-half hours.

7 Q. Is the time element involved
8 in the assay, because we have heard evidence
9 from others as to the length of time it takes them
10 to do an RIA digoxin assay, does that break down
11 according to the component steps that you have to
go through?

12 A. Yes, it does.

13 Q. Very briefly, can you tell us
14 what time is involved in each of the steps we have
15 just discussed.

16 A. The pipetting step and the
17 sampling step will vary from a few minutes, if we
18 are only analyzing one sample, to perhaps half an
hour.

19 Q. All right.

20 A. There is then the addition
21 of the various reagents which may perhaps take
22 15 minutes of so. There then has to be an incubation
23 of a half hour period when the digoxin labelled
24 material and the patient digoxin and standards and
25



F-5

1

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

so on come to an equilibrium so there is a fixed half hour period. After adding the charcoal which may take up to five minutes, possibly ten, we allow the charcoal to sit in the tubes for about a further ten minutes. We then transfer them to a centrifuge and we spin them rapidly at high speed for a period of a further ten minutes or thereabouts.

After that we decant and that will depend on the number of samples we have. We decant this supernatant fluid into a second tube and cap it. We then take those and put them on the gamma counter and that process may take 20 minutes on the gamma counter, perhaps. At the end of that we have a result.

Q. And all of those steps, with the incubation process you have described and to the end use of the gamma counter, takes approximately two to two and one half hours?

A. Yes, I think that is about the shortest you would probably do it in. If you just had one sample you may do it a little bit quicker than that.

Q. In that two and one half hours, can you run more than one sample through your assay?

A. Yes.



F-6

1

2

3

4

Q. Is there a maximum number of samples that you can run through in that period of time?

5

6

7

8

9

A. You would not really want to run more than about 20 or 30 samples. On occasion we have to run more than that. We have run about 40 or so, but that would take longer than the two to two and a half hour period.

10

11

Q. So two to two and a half hours for approximately 20 samples, is that it, at max?

12

13

14

15

A. Yes, at the very most.

Q. Now, since March of 1981, Dr. Ellis, has your laboratory and have you personally been involved in conducting all the RIA digoxin assays conducted in the hospital?

16

17

A. No. In 1982 Dr. Soldin was dealing with this.

18

19

Q. Does Dr. Soldin work in a different lab from your own?

20

21

A. Yes, just across the hallway.

Q. Did he take on part of the RIA digoxin assays in 1982, or all of them?

22

23

24

25

A. He took on all of them.

Q. Is that still the case today?

A. No. I think in November, 1982,



F-7

1

2

3

4

5

6

he was under a lot of pressure in that a lot of requests were being directed to his laboratory because of the new therapeutic drug monitoring program and we undertook to assist him by doing the digoxin levels.

7

8

Q. Dealing with the therapeutic drug monitoring program, Dr. Ellis, as I understand it Dr. Soldin is the director of that program.

9

10

11

A. Yes.

Q. When was that program introduced

to the hospital in a formal way?

12

13

A. I think it was sometime last

year.

14

15

16

Q. You have also told me that Dr. Soldin in his laboratory is using a new technique that is new to the hospital, called fluorescent polarization immunoassay?

17

18

19

20

21

22

23

A. Yes.

Q. Can you tell me, Doctor, under

what circumstances today, as you sit here, would

an RIA digoxin assay be requested in your lab

as opposed to one on the new fluorescent polarization

technique. Is there any criteria that applies as

to which technique will be used?

24

25

A. . Basically as of now we just



F-8

1

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

do the routine batch of digoxins. If there are any samples that come in after the routine batch has been done then they are dealt with by Dr. Soldin's laboratory. Recently I believe the fluorescence polarization immunoassay technique had been used for some of those samples.

Q. And by routine samples, you mean samples that come in on other than urgent or emergency basis?

A. Yes. I mean the regular batch, the batch of the majority of samples that come into the hospital.

Q. If a sample came in for an urgent assay or a very quickly performed assay, would that be done in your lab?

A. If we were just about to start our batch it would probably be incorporated into the batch. If it was very urgent and we were not due to start our batch, then it may have been done on the fluorescence polarization system, or if it came after our batch had been completed then it might then again be done by either the fluorescence polarization or possibly by the radioactive procedure.

Q. So there is no hard and fast rule as to which technique would be used. It depends



F-9

1
2 on the timing of the request for the assay?

3 A. To some extent. I think that
4 this is changing a little bit right now. Exactly
5 what is happening right now, I am not sure.

6 Q. I would like you to direct
7 your mind again, Dr. Ellis, for a few moments if
8 you would to the period, July 1980 to March 1981
9 when you were running the RIA assays for digoxin.

10 At that time, on the technique as
11 you were then using it, and as you have described
12 it here today, was there any minimum level below
13 which you could not with confidence say that the
14 test results clearly indicated digoxin?

15 A. There is a kind of long
16 scientific answer to that question, and a short one.
17 If I could perhaps give you the short answer, the
18 short answer was that you can derive a detection
19 limit in a very scientific fashion, but it is also
20 expedient, very often, with radioimmunoassays to define
21 a limit and report levels that are lower than that
22 limit whether they be below than that limit in zero
23 or even possibly slightly negative, report them as
24 under a particular value.

25 During the period of time you are
discussing, that value was set at 0.2 nanograms



F-10

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25

per ml.

Q. That was July 1980 to March
of 1981.

A. In other words if we got an
answer by going through this process of 0.3 or 0.4
then we would have reported that number.

Q. Yes.

A. If we got an answer of 0.2 or
0.1 or 0, we would report "under 0.2".

Q. I see. Is that the same level
that applies today?

A. No. I think it was changed
and I think sometime in early 1981, when essentially
children that were not being treated with digoxin,
when they started to look at blood levels on those
children and it became apparent then, and it had
not been apparent before that, that some patients who
were not being treated with digoxin had small
amounts of digoxin present in their serum as
measured by the radioimmunoassay technique.

I think Dr. Soldin was dealing with
this at the particular time, but, if my recollection
is correct, we consulted with the Toronto General
Hospital and also Mount Sinai Hospital and asked
them what was their lower limit or their cutoff and



F-11

1

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

they said it was around .5 nanograms per ml. So we elected, because there was so much concern about the level of .3 or .4 indicating possible administration of digoxin to a patient who should not have had it, because of all this concern, we elected, for reasons of expediency, if you like, to define our limit as 0.5. So if we got a 0.4 we would report "under 0.5"; or a level of 0.3 we would report at "under 0.5".

Q. You said that you thought that was sometime early in 1981?

A. Yes.

Q. Do you have any recollection today as to when in 1981 the cutoff or the minimum level was changed from .2 to .5 nanograms per millilitre?

A. I believe this reporting process, I think it was January, I think it was when the pre-trial was on.

Q. Are you talking about the pre-trial involving Susan Nelles?

A. Yes -- so that was 1982, was it?

Q. 1982.

A. Okay, I do beg your pardon.



F-12

1

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

Q. Let us go back just a bit then.
You have told us that there was some testing done
on patients in the hospital who were not known to
have received digoxin?

A. Correct.

Q. I think you said there were some
minimum levels of digoxin detected in their blood
although they had not been prescribed digoxin?

A. That is correct, yes.

Q. When was that testing carried
out?

A. I think that testing was
carried out -- I stand corrected -- it was in 1982,
in January, I believe, when the pre-trial was taking
place.

Q. Was it at that time that
the minimum cutoff level for your digoxin assays
was raised from .2 to .5 nanograms per millilitre?

A. It was then that we started
reporting levels "under 0.5" instead of reporting
levels of "under 0.2".

Q. Who conducted, internal to
the hospital, those tests with respect to patients
who had not been known to have received digoxin?

A. At that particular time,



F-13

1

2

Dr. Soldin would have done those particular samples.

3

4

Q. Were you involved in the tests that were conducted on those children?

5

6

7

8

9

10

11

A. At that particular time, no. The only other evidence that perhaps is applicable here is that in 1981, in March, a number of other children who were on 4A and 4B and who were not being treated with digoxin had their levels measured, and at that particular time quite a large number of them, when we were assaying them, gave us values of under 0.2.

12

13

Q. Those were children that were on the cardiac wards?

14

15

A. The cardiac wards at that particular time, yes.

16

17

Q. I believe you said March of 1981?

18

19

A. March of 1981, yes.

20

21

22

Q. Talking about the testing that was done in 1982 --

23

24

25

A. Right.

Q. Do I take it then that you had no personal involvement in conducting those assays?

A. That is correct, yes.



F-14

1

2

3

Q. Are you familiar with the
results of the testing that was done by Dr. Soldin?

4

5

A. In broad terms, yes, because
I was asked about it at the preliminary hearing.

6

7

8

9

10

Q. We are going to hear from
Dr. Soldin later, Dr. Ellis, he will be testifying,
but can you help us as to your understanding of
what the highest level of digoxin reading was that
he obtained on those patients who had not received
digoxin?

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25



G/BB/ko

1

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

THE COMMISSIONER: These are the patients who did not have digoxin prescribed?

MS. CRONK: That's correct, Mr. Commissioner.

THE WITNESS: Yes. These are actually very young children, young babies on Ward 7F; I think it was 7F - 7E or 7F where there was a problem. Because the source of that problem had not been ascertained at that particular time, digoxin levels were measured just to ensure that the levels were not exceptionally high.

MS. CRONK: Q. Do you know what the highest level was that was recorded by Dr. Soldin on those tests?

A. I believe the highest level was approximately 1.2 to 1.3.

Q. Nanograms per millilitre?

A. Nanograms per millilitre.

Q. Do you know how many children were tested?

A. Not offhand, but I think it was of the order of 20 or 30, possibly more.

Q. And that's a question I can ask of Dr. Soldin?

A. Sure.



G 2

1

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

Q. All right. Let me ask you this then, Dr. Ellis, in light of this information. Have you personally, since March of 1981, been involved in conducting digoxin assays in your laboratory on children known by hospital personnel not to have previously received digoxin since March of 1981?

A. We analyzed a number of sera - do you mean autopsy samples or do you mean --

Q. No, ante mortem samples.

A. Ante mortem samples. Basically we analyze a serum because somebody requests that we analyze the sera. We don't know the exact details of the patient history or whether or not the patient had been on digoxin. We just analyze the serum in many cases.

Q. Well, let's back up and take this in two time frames, Dr. Ellis. Let's start with the period July of 1980 to March of 1981.

A. Okay.

Q. You have just told me that you don't necessarily know whether digoxin has been prescribed for the patient when you're asked to do an assay on the serum. During that time period when a specimen came into your laboratory for testing, would you know, for example, the drugs that had been



1
G 3 2 prescribed to the patient from whom the sample had
3 been taken?

4 A. No, we wouldn't.

5 Q. All right. Would you know the
6 time at which the last - assuming digoxin had been
7 prescribed for the patient, would you know - first of
8 all, would you know that fact, that digoxin had been
9 prescribed? Would you know that?

10 A. No, we wouldn't.

11 Q. All right. But for the purposes
12 of the monitoring of the drug level, for the purposes
13 of running your assay, I take it you assumed that
14 digoxin had been prescribed if you were being asked
15 to do a digoxin assay?

16 A. Yes, it was reasonable to assume
17 that the physician who was requesting the test had good
18 reason for requesting the test; in other words, the
19 patient was on digoxin.

20 Q. All right. So, you wouldn't
21 know whether (a) digoxin had been prescribed or indeed
22 what other drugs may have been prescribed to the
23 patient?

24 A. No, no.

25 Q. If digoxin had been prescribed,
would there be any information provided to you before



G 4

1

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

conducting your assay as to the time at which the last dose of digoxin had been administered?

A. No, not at that time.

Q. Again, that time being July of '80 to March of '81?

A. Correct.

Q. Would you know, for example, again if digoxin had been administered the amount of the last dose?

A. No.

Q. Would you have any information at all as to the time at which the sample had been taken?

A. Yes, we would.

Q. You would know the time at which the sample had been taken?

A. All samples should, when submitted to the laboratory, have the time of the sample clearly stated on the sample requisition, the paperwork that comes with the sample.

Q. And as you didn't know the time at which the last dose of digoxin was administered, I would be correct, would I not, that you couldn't relate the time that you knew the sample to have been taken to the time of the last dose of digoxin because



1
G 5 2 you didn't know one of those facts?

3 A. No, but there were clear
4 instructions in the hospital that digoxin should be
5 taken 5 to 8 hours or thereabouts after the previous
6 dose at that time.

7 Q. Again, you are saying during
8 the period of July '80 to March of '81 there were
9 instructions in the hospital the digoxin samples for
10 assay testing were to be taken 5 to 8 hours after the
11 last dose has been prescribed?

12 A. Correct.

13 Q. All right. Would there be any
14 indication on the requisition form that you received
15 as to when the sample was in fact taken in relation to
16 when the last dose had been prescribed?

17 A. No.

18 Q. Right. So, would it be fair to
19 say you would again have to assume that it was taken
20 within that 5 to 8 hour period?

21 A. That's correct, yes. What might
22 happen, for example, is if we were to find a high level
23 then perhaps we would contact the floors and find out
24 from them exactly when the sample was taken in relation
25 to the dose.

Q. But you would only do that,



1

G 6

2

Doctor, I take it if it was at an exceptionally high level?

3

4

A. Under exceptional circumstances, yes.

5

6

Q. There was something in the level to indicate that that should be done?

7

8

A. Yes.

9

Q. Something in the height of the level?

10

11

A. Yes, otherwise we assume that people knew what they were doing, they were taking the sample at the right time and they were submitting the sample to us.

12

13

14

Q. And when you say, Doctor, that there were clear instructions as to the hospital as to the time period within which a sample from a patient should be taken who is on digoxin, were those instructions recorded in writing?

15

16

17

18

A. The Resident's Handbook I believe states something to that effect. That was published in 1979.

19

20

21

Q. Well, perhaps, Dr. Ellis, I can come back to that.

22

23

A. Sure.

24

25

Q. And you can take an opportunity



1
2 to look at that, if you would be kind enough to do
3 so, at the break. One other piece of information,
4 Dr. Ellis.

5 A. Excuse me.

6 Q. I am sorry.

7 A. The Resident's Handbook states:
8 "Digoxin 0.5 mils of clotted blood.
9 Take blood 6 to 8 hours after last
10 digoxin dose."

11 THE COMMISSIONER: What's the date of
12 that, Doctor?

13 THE WITNESS: This is actually
14 published I believe in 1979 Your Honour.

15 MS. CRONK: Q. And that's described
16 as a Resident's Handbook?

17 A. Of Pediatrics, yes.

18 THE COMMISSIONER: Well then, all of
19 the samples during the relevant period I take it were
20 taken, or should have been taken --

21 THE WITNESS: There was instructions
22 to do that, yes.

23 MS. CRONK: Q. Would you know again
24 in this time frame that we're talking about, Dr. Ellis,
25 the site from which the sample had been taken in the
body?



1
2 A. Not from an analytical point of
3 view. From a point of view of interpretation, yes,
4 but from a strictly analytical point of view, we
5 receive a sample and we analyze it and then we assess
6 whether the result that we have produced is an
7 appropriate result analytically.

8 Q. Right.

9 A. Now, the next question is, is
10 it therapeutic or what is the clinical implications of
11 this particular result, which is a different issue.

12 Q. In terms of assessing whether or
13 not the level is an appropriate one, which I think was
14 the first analytical step you just described?

15 A. The level is an appropriate one?

16 Q. An appropriate one I think was
17 the word you used.

18 A. You mean the level that we have
19 produced is analytically as correct as we possibly can
20 produce it?

21 Q. Fine.

22 A. Okay.

23 Q. With that information, that is,
24 the time at which the last dose of digoxin had been
25 prescribed and the amount of it had been relevant to
you in making that determination?



1

2

A. No, no.

3

Q. There would be no indication of
that on the requisition form?

4

5

A. Not at all, no.

6

Q. All right.

7

A. Except that perhaps the
requisition may have been marked "Arterial" or
possibly "Venous". That indication may have been
given to us. Very occasionally somebody may have
indicated if it was taken from some other source, but
it would be very unusual for that to occur. In general
we wouldn't know.

10

11

12

13

Q. Is there any indication in the
Resident's Handbook or any direction or suggestion to
the residents contained in the handbook as to the
appropriate site from which to take a digoxin sample
for purposes of an RIA assay?

14

15

16

17

A. No there isn't, no.

18

Q. All right. To your knowledge,
quite apart from any direction or indication in the
Resident's Handbook, were there standing instructions
of which you were aware which applied in the hospital
during this period of time as to the site from which
an ante mortem sample for a digoxin assay should be
taken?

19

20

21

22

23

24

25



1

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

A. Perhaps if I could back up a little bit. In relation to digoxin, the Resident's Handbook did not give specific instructions to the specific site from which the sample should be taken.

Q. Yes, that's what I understood you to say.

A. Yes. In other parts of the Handbook, there are various instructions as to how one may obtain blood samples from various parts of a child and, you know, there is usual practice.

Q. What was your understanding as to the usual practice that applied with respect to taking a sample for digoxin assay at that time?

A. This would be taken either from a vein in the arm or perhaps a vein in the scalp, depending on the size of the child, possibly by puncture of the finger or the heel.

Q. And as to which of those had in fact been utilized, that would be a matter that you would not know when you were running the assay unless it was disclosed on the requisition?

A. Yes. We may have some guide to that from looking at the sample itself. In other words, if it comes in a small tube, we may assume that it is a capillary sample rather than coming in a syringe when



1

2

we may assume that it's been taken by vena puncture.

3

4

5

6

Q. Well, whether it came up to your lab in a syringe or whether it came up in a tube, would there be any indication on either syringe or the tube as to the site from which the sample was taken?

7

8

A. In general, no.

9

10

11

12

13

Q. There was no requirement that that be done?

A. There was no requirement, no.

Q. And similarly, am I correct, there was no requirement that the lab be informed on the requisition form as to the site from which the sample had been taken?

14

15

16

A. There was no real requirement or even reason for advising the lab why this should be done, in my view.

17

18

19

20

21

22

23

Q. Doctor, I would like to explore this with you for a moment if I may.

As I understand your earlier evidence, you have told us that the purpose of performing digoxin assays in the hospital during this period of time was effectively to assist in the determination of whether or not a particular dosage of digoxin was or was not appropriate for any given patient.

24

25

A. That's correct.



1

2

Q. Is that correct?

3

A. Yes.

4

5

6

7

8

9

10

11

12

13

Q. Now, as a biochemist, either performing those assays or - clinical biochemist either performing those assays or directing others in the performance of the assays, would it have assisted you in terms of allowing you to place more confidence in the results of the assays had you known the time of the last prescribed dose of digoxin, the amount of the dose and the nature or identity of other drugs that had been prescribed to the patient? Would that information have been of assistance to you in assessing the results that came off your digoxin assay?

14

A. In assessing the results in an analytical point of view?

15

16

Q. Yes.

17

A. This wouldn't have been of any major interest to us, no.

18

19

20

21

22

23

24

25

Q. All right. Now, Doctor, in terms of the particular level, be it any level that the assay produced for you after you completed the digoxin assay, would it be of any relevance to you as the person conducting or supervising that test, to know, for example, the time at which the last digoxin dose had been administered?



1

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

A. In most instances, no. If we had obtained a result of 1.0 and the patient had not had digoxin for the past month, then clearly that would suggest to us that perhaps there was an analytical problem in the assay, or that perhaps we were measuring substances other than digoxin. But from a point of view of assessing whether or not the result is correct or not, there is a process that one would go through. Should I go through that process?

Q. Please.

A. Basically most samples, the majority, if we have sufficient sample, are analyzed in duplicate. This means that you obtain essentially two answers that should be fairly close together. Secondly, from the shape of the standard curve, you can get some kind of an idea as to whether the standardization procedure has worked satisfactorily in that particular assay. Thirdly, from the actual numbers that you obtain, the actual values that you obtain from the quality control sera that you put through the assay --

Q. That's the control samples?

A. The control samples.

Q. Yes.

A. From the values that you obtain



1
2 on those, you can then get a handle on whether the
3 analytical process has been accomplished satisfactorily.
4 So that we have all these things pointing to whether
5 we've got "the right answer or not".

6 Q. Doctor, in addition to that
7 quality control check - is that a fair to describe
8 what you have just outlined?

9 A. Yes.

10 Q. In addition to that, if you, as
11 the individual conducting the assay, or supervising
12 the assay, knew that a particular patient's sample had
13 been taken in close proximity to the time of the last
14 administration of digoxin, would that be of concern to
15 you in terms of assessing, from an analytical point of
16 view, the accuracy of your results?

17 A. No.

18 Q. I see.

19 A. Because you would just obtain a
20 higher result. But of course the interpretation of that
21 result is, as I indicated, a different process.

22 Q. In dealing with the potential
23 for producing high results on the digoxin assay,
24 Doctor, again, during the same period of time that
25 we're talking about, July of 1980 to March of 1981,
was there a maximum limitation in terms of the ability



1

2

of the assay to identify an amount of digoxin? Was
there a maximum beyond which the standards would not
permit identification of a known amount of digoxin?

3

4

5

6

7

A. Yes, basically we could only
go as high as the highest standard that we had tested
because you don't know the exact shape of the curve
above that level.

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

Q. And the highest standard that
applied then from July of 1980 in terms of concentration
of digoxin in the period July of 1980 to March of 1981
was what?

- - - -



H/DM/ak

1

2

A. It was 5.0.

3

Q. So if you got a reading at the

4

end of your assay that was a high reading, am I

5

correct that it would record at the stage of that

6

first assay nothing higher than 5?

7

A. Nothing than 5. Now, 5 was

8

the stated value produced by the Corning Company

9

and with which the standard material was labelled,
okay.

10

Q. So the fact that was the

11

maximum which may be registered the first time you

12

did the assay, am I correct, was a function of the

13

pre-prepared standards that you purchased

14

commercially?

15

A. Yes.

16

Q. That was the highest that

17

would have been calibrated on one run of the assay?

18

A. That is correct. Perhaps,

could I qualify that?

19

Q. Yes.

20

A. Basically I think later on I

21

may be asked about greater than 4.7, greater than 4.8,
greater than 4.9 and perhaps greater than 5.

22

Basically, I think what I would say is that although

23

a decision is not taken lightly in regard to taking

24

25



H2

1
2 the claimed values that a manufacturer supplies you
3 with, and assigning your own values to the standards
4 provided. As a result of a lot of quality control
5 checks on sera from different companies, we were
6 of the opinion that in our particular assay the
7 Corning standards as supplied would produce a more
8 appropriate answer if we in fact called the 5.0
9 standard 4.8 or 4.7.

10 Q. Are you saying then, Doctor,
11 that the standards which you used in the spirit
12 of time was, the highest one, was according
13 to the supplier a .5 concentration?

14 A. 5.0.

15 Q. I am sorry 5.0.

16 A. Yes, 5.0.

17 Q. And in terms of your own
18 assessment as to the reliability of those standards,
19 your lab, or you were of the view that it would be
20 more appropriate to use 4.8?

21 A. Yes, or 4.7 I think in that
22 particular case.

23 Q. Now, Dr. Ellis, if you ran a
24 digoxin assay and the reading came off at 4.7, or
25 4.8, what would you do with a reading of that
level?



1

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

A. Yes. We would report, if we were defining the top standard supplied to us by Corning as 4.7, we would not report a result greater than 4.7 on that particular occasion. In other words, if the computer, or if our graph showed us that 5.2 was obtained we would say greater than 4.7.

Q. Would that result in any circumstances in a dilution in the running of another assay on the sample?

A. Yes. If the sample was high, higher than 4.7, then it was our policy, if the amount of sample permitted to reanalyze that on the next batch.

Q. And to do that you would dilute the remaining amount of the sample that was available to you?

A. That is correct.

Q. Would I be correct then that if there was an insufficient amount of sample provided to you that dilution may or may not be possible?

A. That is correct.

Q. In that sample?

A. Yes.



1

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

H4

Q. Were there any guidelines that applied in your lab as to the number of dilutions that were done as a matter of usual practice if a reading of 4.7 or higher was achieved in a digoxin assay?

A. It would be our usual practice to dilute one in two, so that our next reading would go up to about 9.4 or 10.0. Usually that would catch most sera.

Q. Am I correct that if you got a reading of 9 you would then look at again diluting, assuming there was a sufficient amount of sample?

A. No, if you got a result of 9 you would then report that result of 9, or you would not go any further. If on the other hand, you got a result in excess of 10, or in excess of 9.4, depending which value of the standard you were using, you may then go further if the serum sample permitted you to do that.

Q. What minimum amount of patient sample do you require in terms of volume to run an RIA digoxin assay at all?

A. Yes, to put into a single tube the amount of serum that we would need, or plasma that we would need is 50 microlitres. In other words,



H5

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25

1/20th of 1 NML.

Q . Was that true then in the
period July 1980 to March '81?

A. Yes. As I previously indicated
it was our usual practice wherever possible, and in
the majority of cases, to analyze the samples in
duplicate.

Q . Yes.

A. So we would have two tubes
each with 50 microlitres in and that would make 100
microlitres in total.

Q . But you could do an RIA digoxin
assay on 50 only if you did one run through?

A. We, on some occasions had to do
this, yes, because so little sample was provided.
Clearly the confidence in the result depends on how
many times you have done it, and so we would have
slightly less confidence in a single tube result than
in a result which had been produced as a result of
two tubes.

Q . Dr. Ellis, you have told us
about the kinds of information that were not
available to you in the period July 1980 to March 1981
in running these assays. Sitting here today, is
the information that is provided to your lab when a



1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25

H6

request comes in for digoxin assay any different than the information that was provided to you during that period of time?

A. As of now?

Q. Yes.

A. Yes. As of now, when the therapeutic drug monitoring program was started a different requisition from the usual biochemistry requisition was printed. Because of the importance of assessing the relationship of the results to the time of last dose and the amount of last dose, the interaction with other drugs, much more information is provided on therapeutic drug monitoring requisition.

Q. Do you, for example, Dr. Ellis, when you receive one of the new forms of requisition, do you for example know the time at which the last known dose of digoxin was administered?

A. That is indicated on the requisition.

Q. And I take it, do you know as well whether or not the patient is in fact receiving digoxin, is that indicated on the form?

A. Well, if the last dose is given that indicates digoxin.



1

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

H7

Q. I'm sorry, I was separating the two perhaps. I should have done it in reverse order.

A. Right.

Q. On the new requisition forms that you receive in the lab are the drugs that are prescribed to the patient including digoxin outlined?

A. Yes, I believe that to be the case, yes.

Q. That would include drugs other than digoxin that have been prescribed to the patient?

A. I think in many cases this information is given, yes.

Q. And do you as well, if you are told the time at which the last known dose of digoxin was administered, are you as well told the amount of the dose?

A. I think that there is a space on that requisition for that information to be provided, and I believe in the majority of cases this information is provided. On that requisition there are certain areas that must be filled in and certain areas where, for therapeutic drug monitoring purposes, it is desirable that that information be



H8

1

2

given and the exact - I think it is best to ask
Dr. Soldin about that.

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

Q. Well, Dr. Ellis, let's be
clear about this. As I understand what you told us
earlier the therapeutic drug monitoring program in
a formal fashion came into the hospital, in effect
in the hospital some time last year, is that correct?

A. Yes.

Q. Now, inasmuch as you are running
RIA digoxin assays today in the hospital, do you
do so under the auspices of the therapeutic drug
monitoring program?

A. Yes. They are responsible for
obtaining samples or receiving the samples and just
passing on to us a serum sample for analysis, plus
the requisitions.

Q. And are all assays that are
done for digoxin done under the auspices of that
program now in the hospital?

A. Yes, they would be, yes.

Q. So the revised form of requisition document that you have described for us is one
that would now come into your lab and with which you
would be familiar if you were requested to do an RIA
digoxin assay?



1

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

A. With which I am familiar?

Q. Do you receive them in your lab?

A. We do receive them, yes. I don't usually, it is not my usual habit to look at them in great detail.

Q. There are others in the lab presumably who do that.

A. Who would do that and who would transcribe the patient information into a second book that I would look at in more detail.

Q. Dealing then with the information that comes to your attention, whether it derives from the requisition form or whether it arrives from the transposition of that information into another book, are you provided with information as to the site from which the patient sample has been taken?

A. I think in broad terms, whether it is arterial or venous. The exact site, I don't know whether that is given on the requisitions. Perhaps you could ask Dr. Soldin about that.

Q. That is a very appropriate suggestion and perhaps I would do that.

THE COMMISSIONER: Would it also be appropriate to consider a break at this point?



1

2

MS. CRONK: Thank you, Mr. Commissioner.

3

THE COMMISSIONER: Can you tell me

4

how long?

5

MS. CRONK: I have one last question

6

on this particular area, and with your indulgence

7

could I ask that?

8

THE COMMISSIONER: All right, let

9

us have that.

10

MS. CRONK: And then after that

11

I would expect about half an hour, 20 minutes to

12

half an hour.

13

THE COMMISSIONER: Yes, all right,

let's have the last question.

14

MS. CRONK: Q. My last question in

15

respect of that, Dr. Ellis, is can you help us as

16

to when these revised requisition forms came into

17

place in the hospital?

18

A. With the therapeutic drug
monitoring program.

19

Q. Around the same time?

20

A. Yes.

21

Q. Thank you.

22

A. And then there was a subsequent
revision of the requisition.

23

Q. Perhaps we will deal with that

24

25



1
2 after the break.

3 A. Sure.

4 MS. CRONK: I apologize,
5 Mr. Commissioner, for neglecting the time.

6 THE COMMISSIONER: That is all right.
7 We will take 15 minutes.

8 ---Short recess at 11:40 a.m.

9 ---Upon resuming at 11:55 a.m.

10 MS. CRONK: We seem to be missing
11 a few counsel, Mr. Commissioner. I am prepared
12 to recommence or I can search them out.

13 THE COMMISSIONER: The nice thing
14 about having Commission is that if we are missing
15 counsel we just go right ahead. It is not considered
16 good form at a trial but I can't believe anything
17 in the Public Inquiries Act that says I have to wait
18 until counsel have finished their coffee.

19 MS. CRONK: There is one exception
20 to that, Mr. Commissioner, but I won't dwell on that.

21 THE COMMISSIONER: All right.

22 MS. CRONK: Q. Dr. Ellis, immediately
23 before the break you told us that the form of
24 requisition that is currently in use for digoxin
25 assays again has recently been revised, is that
correct?



1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25

A. Yes, you mean in relation to the standards?

Q. Well, I don't know what you were referring to. You suggested just before we left at the break that the form of requisition ---

A. Oh, yes.

Q. --- had again been revised.

A. Yes.

Q. I take it that was a revision subsequent to the date of introduction in the hospital of a therapeutic drug monitoring program?

A. Yes.

Q. Now, is the kind of information that we were discussing prior to the break still disclosed in the requisition forms that are now provided to your lab?

A. Yes.

Q. Is any additional information particular to the patient sample provided that was not previously provided?

A. I don't know.

Q. You also told us before the break, Dr. Ellis, that for your purposes in assessing analytically the results of the digoxin assay it was not necessary for you to know and was not



1
2 relevant for you to know, for example, the time of
3 administration of the last digoxin dose, the amount
4 that had been administered, or the amount of
5 drugs that the patient was prescribed, do I have
6 that right?

7 A. Yes.

8 Q. And I take it you to mean by
9 that that for interpretation of the results it may
10 be necessary, but for your purposes that information
11 is not ?

12 A. Yes. Just as Dr. Seccombe
13 mentioned yesterday, he was supplied with informa-
14 tion and it helped him to discover any problems in
15 his assay. Okay. By accident something happened
16 that the patient who was not on dig, had dig
17 measurement, and so in the unlikely event that this
18 information was provided to us something may come
19 from that, but it is not absolutely essential.
20 from an analytical point of view.

21 THE COMMISSIONER: Can I just ask
22 how much interpretation did you do? I know you did
23 the analysis?

24 THE WITNESS: Yes.

25 THE COMMISSIONER: How much did you
do to determine what the level was, what did you do



1
2 after that? Supposing the level did turn out to
3 be what you considered a toxic level, did you do
4 anything about it, or do you report that to the
5 doctor in charge?

6 THE WITNESS: It was our policy I
7 believe at that time that all digoxin results,
8 irrespective of whether they were normal or abnormal,
9 would be telephoned to the floors as soon as they
10 were available. In addition a computer report
11 would be produced so that written information would
12 follow.

13 THE COMMISSIONER: I am just
14 wondering what action you took, you or your staff
15 took with regard to it? Is that what you did,
16 merely report the results?

17 THE WITNESS: We reported the
18 results. In some instances, and I wouldn't like
19 to say this happened in every case, in some instances
20 if something very unusual had occurred then I might
21 go onto the floors and ask about what has happened,
22 or I might telephone the floors.

23 THE COMMISSIONER: That would be
24 a very high reading?

25 THE WITNESS: Yes.

THE COMMISSIONER: That would be very



1

2

unusual?

3

THE WITNESS: Yes.

4

5

THE COMMISSIONER: Can you remember
any instance of having done that?

6

7

8

9

10

11

12

13

14

15

THE WITNESS: I can remember
several instances where unusually high readings were
found and I did visit let's say the Intensive Care
Unit and occasionally four A, and in the majority
of instances I would have been assured that the
sample had been taken perhaps very shortly after
the dosage had been given, this kind of information,
but I wouldn't like to say that in every single case,
every single result, all those results I immediately
took action at that time, but in many instances that
was the case.

16

17

18

19

THE COMMISSIONER: Well, really
what I was getting at, did you consider it was
your responsibility, or was it the responsibility
of the attending doctor to do something about a
toxic reading?

20

21

22

23

24

25

THE WITNESS: Yes, we regarded it,
as soon as we had telephoned that abnormal result,
or that normal result to the floors of the hospital
just as it was the responsibility of the attending
physician to obtain this sample at the time that



1
2 he felt was appropriate and for the clinical indica-
3 tions that he felt were appropriate, we felt that
4 it was his responsibility to take action on the basis
5 of the result that we have provided to the floors.

6 THE COMMISSIONER: All right, thank
7 you very much, Doctor. I am sorry, Ms. Cronk.

8 MS. CRONK: Thank you, Mr. Commissioner.

9 Q. Just a couple of questions
10 following upon that, Dr. Ellis. Perhaps you see
11 the problem I am having with respect to the provi-
12 sion with this kind of information to you.

13 A. Okay.

14 Q. If the information is not
15 required by you and is not relevant for your
16 purposes, can you help me as to why with the
17 introduction of the therapeutic drug monitoring
18 program it was determined and desirable that
19 that information now be provided directly to the
20 lab?

21 A. Yes. Basically so that the
22 results that are provided can be interpreted and
23 it is possible that one doctor might request a
24 test knowing perhaps when a particular administra-
25 tion has been given of digoxin to a child.



I-1

1

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

Perhaps the result becomes available at a time when that doctor is not immediately available on the floor and, under those circumstances, a new doctor would have not only the result that he would have in a computer format a clear indication as to when the last dose was given and what the dosage was.

Q. I see. So it is provided then for the assistance of whoever the individual might be who is going to interpret the results.

A. That is correct.

Q. That, I take it, is not the province of yourself or those others who you supervise in your lab?

A. That is correct, yes.

Q. But as a byproduct of the provision of that information it may or may not prove to be useful to you?

A. Yes.

Q. Thank you, that does clarify it.

In response to one of the questions put to you by the Commissioner you indicated, I believe, that test results were communicated directly to the floor as soon as they were available. Is that correct?



I-2

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25

A. That was the case in 1980
to 1981.

Q. That is the time period for
the moment that I am interested in.

Can you tell me, I know you said
as soon as they were available -- you have also
told us that the approximate time required to do an
RIA digoxin assay was two to two and one half hours.
Was there any policy that applied during that period
in your lab as to how soon after the completion of
the assay those results were to be communicated to
the person requesting the test?

A. Yes, when those results were
ready, they were communicated to the floors.

Q. How were they communicated?

A. By telephone.

Q. By telephone?

A. Yes.

Q. Was that so, regardless of the
levels that the assay produced?

A. At that time, yes.

Q. Be it a low one, a medium-range
or a high one?

A. Yes.

Q. Whatever the result?



I-3

1

2

A. Yes.

3

Q. You also mentioned a few

4

moments ago a computer summary that is now provided

5

to the physician who requested the test showing

6

both the level result and the other information that

7

was originally provided to the lab?

8

A. Yes.

9

Q. Was there a computer printout

10

or a computer summary with respect to your assay

11

results in the July 1980 to March 1981 time frame

12

that was provided back to the requesting physician?

13

A. There was a computer result,

14

yes, and that was provided the following morning,
essentially.

15

Q. The morning after the assay

16

had been completed?

17

A. That is correct.

18

Q. Not the morning after the sample

19

had been received by the lab, necessarily?

20

A. Usually the morning after the

21

sample had been received by the lab simply because

22

the digoxin result in the patient would be taken

23

in by the computer, would be fed into the computer.

24

Any electrolite results on the same patient, any

25

of the tests on blood samples on that particular



I-4

1

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

patient, would go into the computer. The computer would then check to see whether it had had any previous results on that particular patient and would then produce a cumulation of all this information including the digoxin which would be available next morning.

Q. I see.

A. There is a lot of computer time involved in that process of producing a cumulative report.

Q. I am operating on an assumption here, Dr. Ellis, that may in fact be incorrect, and this is I have been assuming that when your lab was requested to run a digoxin assay on a particular patient sample that was a request that came to you from a physician in the hospital. Is that correct?

A. Yes, through the main biochemistry laboratory generally.

Q. And we were talking in that context ante-mortem samples?

A. Yes.

Q. With respect to the information that was provided back to the floor, you have told me about the computer summary, it was a cumulative kind of information base as I understand it and it



1

2

included information with respect to other assays
that have been run, quite apart from the assay
on digoxin. Is that correct?

4

5

A. Yes.

6

7

8

9

10

Q. When a requisition, again
talking the time frame July 1980 to March 1981, when
a requisition came into your lab requesting a
digoxin assay, would that requisition also disclose
whether or not other assays on other drugs had been
requested in respect of the same patient sample?

11

A. In the majority of instances, no.

12

13

14

Q. So you would not know when
you were doing a particular digoxin assay whether
an assay for any other drug was also being done?

15

A. No.

16

17

Q. Under today's conditions, under
the Therapeutic Drug Monitoring Program, is that
information disclosed on the requisition form?

18

A. I think it may be.

19

20

21

22

23

24

25

Q. Perhaps, Dr. Ellis, and
Mr. Commissioner, with your concurrence, I propose
that we reserve an exhibit number, because I
do not have a copy of the requisition forms that
Dr. Ellis has been referring to, and perhaps
his counsel could provide them for future



I-6

1

2

3

4

identification and marking as an Exhibit, with the three requisition forms that you have been discussing.

5

6

7

8

9

10

11

As I understand it, the first is the requisition form that applied during the period July 1980 to March 1981; the second, and correct me if I am wrong, Dr. Ellis, is the form of requisition that was introduced with the introduction of the Therapeutic Drug Monitoring Program; and the third is the requisition as revised that is currently in use pursuant to that program.

12

Do I have that correctly, Dr. Ellis?

13

14

A. Yes, I think it would be possible to provide that information.

15

16

THE COMMISSIONER: Do you have those as well, Mr. Roland?

17

18

MR. ROLAND: Yes, I have taken those down.

19

THE COMMISSIONER: Do you accept the mandate?

20

MR. ROLAND: Yes, sir, I do.

21

22

MS. CRONK: May we reserve a number then, Mr. Commissioner for that purpose.

23

24

THE COMMISSIONER: All right, what number do we have -- Exhibit 15.

25



I-7

1
2 ---EXHIBIT NO. 15: (reserved) Three requisition
3 forms: form in use during period
4 July 1980 to March 1981; form
5 introduced with the Therapeutic
6 Drug Monitoring Program; and the
7 form currently used by the
8 program.

9 MS. CRONK: Q. Dr. Ellis, we were
10 discussing as well before the break the circumstances
11 in which you would do a further dilution of a
12 patient's sample, and again I would like to talk
13 about the July 1980 to March 1981 time period.
14 You told me that if on the first assay run you got
15 a result of 5 or 4.7 or 4.8 to 5, you would dilute
16 usually one to two and do another assay, right?

17 A. Yes, correct.

18 Q. As I understand your evidence
19 you also told me that if the result on that second
20 assay run was 9.7 plus you would not automatically
21 do another dilution and another assay run. Is
22 that correct?

23 A. We would probably go further
24 than the 9.7 plus, yes.-- you asked me about 9.0,
25 and I said --

Q. Sorry, I misunderstood.

If, on doing the first dilution and
therefore the second assay test run on the same
sample, you in the end result obtained a level, is



I-8

1

2

it 9.7 -- what is the bench mark from which you would
feel it appropriate to do a further dilution?

3

4

A. If we had done a one and two
dilution?

5

6

Q. Yes.

7

A. Then if you took the current
highest standard available and multiplied that
number by 2 that would give you the level above which
you would endeavour to dilute, perhaps one in five.

8

9

10

THE COMMISSIONER: You would
invariably get a figure under 5, but you would
multiply it by 2 to get the results, because of
the dilution, is that right?

13

14

THE WITNESS: Yes.

15

THE COMMISSIONER: Because your
apparatus won't read more than 5?

16

17

THE WITNESS: Not accurately, no.
It may give you an actual printout slightly greater
than 5 but you could not rely on that number.

18

19

MS. CRONK: Q. In response to the
Commissioner's question, as I understand it, Dr.
Ellis, you told us earlier that for your purposes
internal to your lab that you would adjust the 5
nanogram concentration set by the standards supplier
to 4.7 - 4.8?

23

24

25



I-9.

1

2

3

A. Over part of the period that we have discussed.

4

5

6

7

Q. If that were the case and you did a first dilution on a 1 to 2 basis, do I take it then that if you got a result of 9.4 you would automatically do a second dilution?

8

9

10

11

12

13

14

A. Yes, I think that is correct to say that we would automatically do that. It is difficult to say for sure that we would do that because we are dealing with a toxic level by the time we get to 9.4. As a result of a toxic level being reported, the patient's physician should withhold the next digoxin dose, if that sample has been collected under appropriate conditions.

15

16

17

18

19

20

21

22

A. So whether from a clinical therapeutic drug monitoring purpose, whether we report a 9.7 or a 13.3 it is still too high, if that sample has been appropriately collected. So the net result will be that the next digoxin dose, after that report, will be withheld and possibly subsequent ones too, until the level is at a more satisfactory basis.

23

24

25

Q. Dr. Ellis, I do not want to involve you in an area which is outside the area of



I-10

1

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

your particular expertise, but you have just told me that if a 9.4 result were achieved you are then at a toxic level, with the consequences that you have just described.

Can you tell me, in your mind, in running these RIA assays, from what level would the toxic range commence, as far as you are concerned, in obtaining assay results from digoxin?

A. During which time frame?

Q. July 1980 to March 1981.

A. Yes. At that time I was under the impression that digoxin was given on a daily basis in a similar manner to many other hospitals, -- children's hospitals -- and also in a similar manner to many adult hospitals in the treatment of many adults.

Q. Yes.

A. When digoxin is given on a daily basis it is the usual procedure, according to the literature, to take a sample perhaps six to eight hours after the last digoxin dose.

Q. Yes.

A. Because by that time the peak level that follows the dosage has subsided and although it is not flat it is becoming flatter.



I-10

1

2

Q. You are at a steady state?

3

A. You are at a fairly steady

4

state, yes.

5

Q. Assuming that the sample was

6

taken under those appropriate conditions, what level

7

of reading would be the lowest from which anything

8

over that would be considered in your view to be

9

toxic?

10

A. In preparation for the

11

Residents' Handbook, the section that I was

12

responsible for, I consulted a number of articles,

13

and those articles are a little bit controversial

14

in that no single number is given universally

15

throughout all articles. One article in 1978, in

16

the Journal of the American Medical Association,

17

used the following values. Under 0.5 nanograms

18

per ml is indicative of under-digitalization; 0.5

19

to 2.5 nanograms per ml. is optimal; 2.5 to 3.0

20

nanograms per ml. is overlap and greater than 3.0

21

nanograms per ml. is overdigitalized or toxic.

22

Q. Was that the range that you

23

applied in conducting assays in July of 1980 to

24

March of 1981?

25

A. Yes. This was the value. We

26

would say probably about 2.5 we would be a little bit

27



I-11

1

2

concerned about that particular patient.

3

4

Q. And anything over 3 you would be concerned about?

5

6

7

A. Anything over about 2.5 we would be concerned about because it gets into that overlap area.

8

9

Q. You were referring to an article, Dr. Ellis. Can you identify that for us?

10

11

A. In the Journal of American Medical Association, Volume 239, page 2594, in 1978.

12

Q. Do you have a copy of that with you, Dr. Ellis?

13

14

A. I do not have it with me, no. I am just reading that from the Residents' Handbook.

15

16

17

Q. If it can be done and it is not a matter of inconvenience to you perhaps you could provide a copy of that to us.

18

19

20

21

22

A. Okay. The other issue that perhaps the clinical pharmacologist dealt with on Tuesday, but I think it is important to consider not only simply the measurement itself but also the clinical condition of the patient at the time when that level was measured.

23

24

25

Q. You raise another issue with that, Dr. Ellis. Let me, if I understand what you



I-13

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25

are saying, ask you this. As I understand it the results of a digoxin assay test alone for therapeutic assessment purposes are insufficient. Is that correct?

A. That is correct.

Q. In addition to the assay result, one for therapeutic purposes in a clinical setting has to compare or at least interpret those results in the context of the clinical condition of a particular patient. Is that correct?

A. That is correct.

Q. And it is the two in combination that allows for a judgement to be made as to whether or not a patient is or is not over or under digitalized.

A. That is correct.



1

2

Q. All right, Thank you.

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

26

27

28

29

30

A. If I could perhaps expand on that. The serum concentration above which toxicity, in other words the clinical symptoms present, isn't clearly defined. As I mentioned in some studies 2.5 was regarded as the limit above which toxicity became likely and, in other studies, 2.0 nanograms per millilitre was potentially toxic.

In addition to this, there is a literature which suggests that premature and low birth weight infants appear to tolerate higher levels. The literature also says that they may not benefit from that.

In the light of hindsight, perhaps that literature is confused by the kind of substances that were discussed in this hearing yesterday because basically if you measure substances, perhaps different assays measure different substances, in addition to dig, and so the clinical interpretation of those numbers becomes a little confused.

Q. As the state of the art existed as you knew it, Dr. Ellis, in July of 1980 to march of 1981, I take it that the range that you were concerned with was the one that you described a few moments ago, and, that is, anything over 2.5 nanograms per millilitre



1 on an assay result would be of concern?
2

3 A. Yes.

4 Q. You also indicated, Dr. Ellis,
5 a few moments ago that you were responsible for the
6 preparation or the drafting of part of the Residents
7 Handbook. Is that correct?

8 A. Yes.

9 Q. Can you identify for me what
10 part of the handbook was your authorship?

11 A. Much of the biochemistry
12 section, in collaboration with other people in
13 biochemistry.

14 Q. Did that include the sections
15 of the handbook that described the methodology and
16 the procedures involved for conducting digoxin assays?

17 A. That is not contained in the
18 handbook.

19 Q. All right, thank you. One
20 follow up question as well, Doctor, from your testimony
21 this morning. You indicated I believe that in
22 January of 1982 tests were undertaken by Dr. Soldin
23 at the Hospital in tests, and by tests I mean digoxin
24 assays, in respect of children who were known not
25 to have received digoxin, and you talked about that
26 in the context of the maximum assay reading being
27
28
29
30



Ellis, dr. ex.
(Cronk)

1 adjusted in the tests that you do. Can you tell me
2 why, if you know, why those tests were undertaken by
3 Dr. Soldin?
4

5 A. This was in relation to the
6 problems on the 7th floor that were subsequently
7 discussed at a Coroner's Inquest I Believe.

8 Q. That's why I raise it, Dr. Ellis,
9 because, and perhaps I misheard what you said earlier
10 this morning, but my understanding was that you told
11 me those tests were undertaken by Dr. Soldin some-
12 time, you thought, in January of 1982.

13 A. Yes.

14 Q. After the Preliminary Inquiry.

15 A. During the Preliminary Inquiry.

16 Q. During the Preliminary Inquiry,
17 and I thought prior to that you had referred to some
18 of the results involving that ward as applying in 1981.
19 Are we in fact talking two different time periods or
20 are we talking 1982?

21 A. We are talking two different
22 time periods.

23 Q. All right.

24 A. We're talking two different
25 wards.

26 Q. All right.
27
28
29
30



Ellis, dr.ex.
(Cronk)

1
2 A. In March, 1981 we're discussing
3 the tail end that this Commission is concerned with.

4 Q. Yes.

5 A. For the reasons of patients
6 safety, I guess, and at the request of the Coroner,
7 samples were taken from, I believe for a few days
8 at any rate, all patients on Wards 4A and B, including
9 those patients who had not been prescribed digoxin.

10 Q. And when was that, what time
11 period are we talking about?

12 A. We're talking about March of
13 1981.

14 Q. All right. And then the
15 second time period is January, 1982?

16 A. Right.

17 Q. The period you've described?

18 A. These are the only two periods
19 when, to my knowledge, patients were analyzed - the
20 serum was obtained from patients who were not being
21 treated with digoxin, for the purpose of assessing
22 the methodology and assessing whether such patients
23 might in fact have been treated with digoxin.

24 Q. All right. Now, let's deal
25 then, if we may, with the March, 1981 time frame.
26 I take it we're talking post mortem samples, or are
27
28
29
30



1 we talking ante mortem and post mortem?
2

3 A. We're talking of monitoring
4 all patients on Wards 4A and B.

5 Q. So, ante mortem samples.

6 A. Sure.

7 Q. All right. Now, other than
8 the children, the deaths of the children with which
9 this Commission is concerned, are you talking about,
10 or were ante mortem sample tests done on other
11 children who were known not to have received digoxin?

12 A. Yes.

13 THE COMMISSIONER: I understood you
14 to say all of them.

15 THE WITNESS: All the patients on
16 those wards at that particular time.

17 MS. CRONK: All right. Well, can
18 you help us then, Dr. Ellis, as to when those tests
19 were commenced?

20 THE COMMISSIONER: I guess this may
21 be relevant to this aspect but I would be wary of
22 opening the door to too much cross-examination on
23 what went on at that period at this point.

24 MS. CRONK: I'm sensitive to that,
25 Mr. Commissioner.

26 THE COMMISSIONER: Yes, all right.
27
28
29
30



Ellis, dr. ex.
(Cronk)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30

MS. CRONK: I just would like to at least have a clear understanding in my mind as to whether tests were done on other children who were known not to have received digoxin.

THE COMMISSIONER: Well, as I understand it, in March of 1981 there was a blanket examination of all children, at least all children in the two wards with which we are concerned. Correct?

THE WITNESS: That's correct, yes.

MS. CRONK: All right. Well, that will suffice for the moment, thank you, Mr. Commissioner.

THE COMMISSIONER: Yes, all right.

MS. CRONK: Q. And in the period January of 1982 that we're talking about, those are the tests that you previously described were conducted by Dr. Soldin?

A. Yes.

Q. All right. And that was a different ward?

A. Yes.

Q. All right, that was Ward ...?

THE COMMISSIONER: 7.

THE WITNESS: The 7th floor, 7E or 7F.



Ellis, dr. ex.
(Cronk)

1

2

MS. CRONK: All right, thank you.

3

A. Okay.

4

5

6

7

8

Q. Now, again dealing with the period July of 1980 to March of 1981, Dr. Ellis, as a general matter were post mortem tests for digoxin conducted on cardiology patients during that period of time, as a general matter?

9

A. I think during that time, no.

10

11

12

13

14

Q. All right. And since March of 1981 you have told us that there was a general monitoring of patients on those wards, and do I take it that that included both ante mortem testing and post mortem testing?

15

16

17

A. Well, some of those patients would be treated with digoxin, so, they would be ante mortem testing, yes.

18

19

20

Q. And as well, that included the post mortem testing that you referred to a few moments ago for digoxin?

21

22

23

A. Any children who died on those wards would have had blood taken at autopsy.

24

25

26

27

28

29

30

Q. All right.

A. And, in fact, that was extended subsequent to that period to deal with, from what I understand, all autopsies at the Hospital where blood



Ellis, dr.ex.
(Cronk)

1
2 could be obtained from the children.

3 Q. Are the samples - you have
4 referred now several times to the blood - are the
5 samples that were taken during the July, 1980 to
6 March, 1981 period as a matter of routine for digoxin
7 assays in your lab, were those samples of blood?

8 A. Yes, they would be on blood.

9 Q. And were any samples taken,
10 any tests or assay tests run on tissue during that
11 time period from July of '80 to March of '81?

12 A. Not on a regular routine
13 basis, no.

14 Q. All right. Some were done on
15 an isolated basis?

16 A. Yes.

17 Q. All right. Is the RIA procedure
18 that you have in the Hospital capable in a technical
19 sense of performing assays on tissue samples?

20 A. On the two occasions when we
21 tested it, we obtained quite equivocal results and
22 it was clear that a lot of work would need to be done
23 to modify the method to deal with those samples and
24 in fact, this did not take place.

25 Q. All right. So, I take it then
26 that following March of 1981 tissue sample testing
27
28
29
30



Ellis, dr.ex.
(Cronk)

1
2 for digoxin is not a matter of routine in the Hospital
3 for the very purpose, for that very reason?

4 A. That's correct, yes.

5 Q. Thank you. And when you talk
6 about blood samples, Doctor, are you distinguishing
7 in your mind between whole blood, plasma and serum?

8 A. The material put into the tubes
9 that you have drawn on the diagrams, we wouldn't
10 deal with whole blood, we would centrifuge, we
11 would spin down the blood into its constituent parts
12 and use the clear fluid, either the plasma or the
13 serum in our particular assay.

14 Q. If a sample of whole blood was
15 received by your lab, you have told me that you
16 would centrifuge it and use either the plasma or the
17 serum.

18 A. Yes.

19 Q. Was there any particular preference
20 of guideline that applied as to which you would use
21 for the digoxin assays, plasma versus the serum?

22 A. No. Either would be
23 satisfactory in my view.

24 Q. All right. We've heard
25 evidence as well, Dr. Ellis, and you have told us I
26 believe that you were present in the Courtroom for
27

28

29

30



J 10
/ko

1

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

the evidence of Mr. Cimbura as to an extraction process that may or may not be used at the time when a sample is initially received in the laboratory for the purposes ultimately of the digoxin assay?

A. Yes.

Q. Now, as I understood that evidence, the purpose of the extraction process that applied was to determine how much digoxin was lost, if you will, or, in the converse, retained after the centrifuging of the sample so that you knew the amount of digoxin that ultimately was going to be tested.

Do you, in your laboratory, perform any extraction process on a sample of whole blood that arrives in your lab for digoxin assay?

A. We don't do any extractions in my laboratory.

Q. All right.

A. I don't think the introduction was quite correct to that question though.

Q. Well, it wasn't my intention certainly to misstate the concept, but as I understood it, the evidence that we heard from Mr. Cimbura with respect to the procedures in his lab suggested that there is an extraction process that can be utilized at the time when the sample is originally obtained to



1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25

J 11

essentially purify or filter out undesirable elements from the samples so that you then know the amount of digoxin - I am sorry, you then have a pure component on which to run your assay. I take it you do not perform that kind of an extraction process on the samples that you receive?

A. That's correct, yes.

Q. During the period July, 1980 to March of 1981, did you apply such an extraction process in your lab?

A. No.

Q. All right. And similarly then we heard evidence from Mr. Cimbura as to recovery, what was described as recovery rate studies that might be undertaken with respect to that extraction process to determine the amount of digoxin recovered as a result of the extraction process itself. If you don't do the extraction process for that purpose, would I be correct in assuming that you don't undertake recovery rate studies of that kind?

A. On a routine basis we would not undertake recovery rate studies. I understand that these have been done. But we have other indications that we are measuring all the digoxin that's in the sample.



J 12

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25

Q. All right.

A. From our other studies.

Q. Well, I would like to be clear about this, Dr. Ellis. In terms of a recovery rate study designed to determine the efficiency of the extraction process that applies to determine how much digoxin was recovered by that process, if you don't do the extraction process, am I correct that you would not be in a position to do the recovery rate study that would relate to that extraction process? If you don't do one, you can't do the other?

A. The recovery study in relation to the extraction process, no.

Q. All right. So, clearly, that isn't done in your laboratory either?

A. That's right.

THE COMMISSIONER: You do have some kind of recovery study?

THE WITNESS: It is possible to do a recovery study from plasma to make sure that all the digoxin that is present in the plasma is in fact measured.

THE COMMISSIONER: And the question was did you undertake it?

THE WITNESS: I personally didn't



J 13

1

2

undertake it, no.

3

4

THE COMMISSIONER: No, did anyone
under your care or control?

5

6

7

8

9

10

11

12

THE WITNESS: Nobody under my care
and control undertook it. As I mentioned, I came in
1976 and exactly what happened in 1974 I am not sure
about. I know that subsequent studies have been done
very recently by Dr. Soldin, but on the basis of other
quality control materials that we had analyzed, we had
good reason to believe that we were getting the right
answer and it was not really necessary in my view to
systematically measure recovery studies.

13

14

15

16

MS. CRONK: Q. So that am I correct
then, Dr. Ellis, the recovery studies that you are
speaking of are studies that have been undertaken by
Dr. Soldin and perhaps we can ask him about those?

17

18

A. Sure.

19

20

21

22

23

24

25

Q. You have not been involved in
them?

A. That's right, yes.

Q. And they are not the same kind
of recovery study that would relate to the extraction
process that's used at the beginning of the process to
purify the sample received? They're a different kind
of study?



J 14

1

2

A. The concept is similar.

3

Q. All right.

4

A. In that digoxin is added to a

5

sample and then you assay subsequently and find out

6

how much you appear to have recovered from that

7

addition.

8

Q. And just on that, Dr. Ellis, as

9

I understand it from my review of your curriculum

10

vitae, you have no experience personally in a forensic

11

setting for the conducting of RIA assay tests, is that

12

A. That's correct, yes.

13

Q. And similarly I believe you told

14

me earlier that you do not have any experience with the

15

HPLC method?

16

A. For digoxin?

17

Q. That's right, for digoxin.

18

A. For digoxin, no.

19

Q. All right. And as I understood

20

your evidence earlier as well, the antibodies that you

21

use on the RIA assay in the hospital are purchased

22

commercially from Antibodies Inc. and we've heard in

23

evidence that the antibodies used by Mr. Cibura at the

24

Centre for Forensic Sciences comes from the Beckman

25

Company in a kit?

A. That's correct.



K/DM/ak

1

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

Q. Do you have any experience in running RIA assays for digoxin with the Beckman Antibody?

A. Not at all, no.

Q. And we have heard from Dr. Seccombe that the antibody, one of the antibodies that was used for the purposes of his study was, I believe it was the NML antibody, and that was the one upon which he reported in his letter to the New England Medical Journal. Have you in your experience in running RIA assay tests for digoxin, had any experience with that NML antibody?

A. No.

Q. I take it then you are not in a position, given your lack of experience in a forensic as opposed to a clinical setting, to provide us with your views as to what might or might not be appropriate method of testing for dogoxin in a forensic situation?

A. Yes.

Q. And would you agree with me, would it be fair to suggest, Dr. Ellis, that the purposes for which digoxin assays are conducted in a clinical setting are very different than the purposes for which they are conducted in a forensic



1

2

setting?

3

A. That is correct.

4

5

6

7

8

9

10

Q. Dealing just again with the antibodies that are used in the assays that you conduct. You told me earlier and produced for us a document which indicated the cross-reactant drugs to the antibody that is in use in your RIA assay. Are you using the same antibodies now from Antibodies Inc. that you were using July 1980 to March 1981?

11

12

13

A. We are obtaining them from the same supplier, yes. I believe they are the same lot number.

14

15

16

17

Q. Insofar as you are aware are the same drugs cross-reactant to the antibodies you are currently using as applied to the antibodies you were using in July of 1980 to March 1981?

18

19

20

21

22

A. I suppose, yes.

23

24

25

Q. I believe, Mr. Commissioner, that copies of that exhibit were produced at the break for other counsel. Can you tell me, it might of assistance to you to have it before you, Dr. Ellis.

THE COMMISSIONER: Which exhibit is that that you are referring to?



Ellis, dr.ex.
(Cronk)

1

2

MS. CRONK: Exhibit 14.

3

4

THE WITNESS: Yes, I have a copy,
thank you. This is the 1974 document, is it?

5

6

7

8

MS. CRONK: Q. Yes. I'm sorry,
Dr. Ellis, I have referred to it as Exhibit 14,
the document from Antibodies Incorporated, entitled
"Digoxin Antiserum".

9

10

11

12

13

A. Yes.

Q. Can you briefly identify for
the Commissioner, and you referred to some of
these earlier in your testimony, those drugs indicated
by the supplier of your antibodies to have known
cross-reactivity features to digoxin?

14

15

A. Well, those drugs I have
mentioned before.

16

17

THE COMMISSIONER: I haven't got the
it
exhibit, but didn't/say on the exhibit what they
are?

18

19

20

THE WITNESS: Yes, it said the
specificity related to digoxin cross-reaction which I
understood was digitoxin cross-reaction.

21

22

23

MS. CRONK: Q. I see. So you are
referring just for purposes of clarity, because I
had some difficulty with this, Mr. Commissioner.

24

25

THE COMMISSIONER: I thought that



Ellis, dr.ex.
(Cronk)

1
2 when he was reading it, that he said, that he gave the
3 proportions and almost all of them were negligible.

4 MS. CRONK: Q. That is what I
5 want to clarify, which portion of the exhibit you
6 are referring to when you read those out. Can you
7 help me with that, Dr. Ellis?

8 A. Yes. That is the information
9 supplied by the company in 1974 relating specifically
10 to a method of practice using that antiserum at
11 that particular time. Prior to the Preliminary
12 Inquiry I did make contact ---

13 THE COMMISSIONER: No, I'm sorry,
14 Doctor, I don't think that is the question. The
15 question as I understood it was, and I will have to
16 look at this document ---

17 MS. CRONK: Perhaps I can help you,
18 Mr. Commissioner.

19 THE COMMISSIONER: Where were you
20 reading from?

21 THE WITNESS: Oh, I'm sorry, under
22 "Specifications".

23 MS. CRONK: Is that on the first
24 page under Specifications?

25 THE WITNESS: Yes.

THE COMMISSIONER: The first page?



1

2

MS. CRONK: Thank you.

3

THE WITNESS: That's right.

4

5

6

7

MS. CRONK: Q. And those as I understand it, at least that literature was provided in 1974 from the manufacturer of these antibodies, is that correct?

8

9

A. Yes, I believe that to be the case.

10

11

12

13

Q. I note in reviewing that, Dr. Ellis, that no mention is made of the drug quinidine. Do you know whether or not the supplier tested for cross-reactivity between digoxin and that drug?

14

A. I don't know, no.

15

16

Q. Similarly no mentioned is made of the drug propranolol.

17

18

19

20

A. Propranolol.

Q. Propranolol. Do you know if the supplier or the manufacturer tested for cross-reactivity between that drug and its antibody for digoxin?

21

A. I don't, no.

22

23

24

25

Q. And similarly my recollection of reading it at the break is there is no mention of the drug and I hope I am pronouncing this right,



1

2

furosimide?

3

A. Furosimide.

4

Q. Furosimide. Do you know

5

whether or not the supplier conducted any testing
6 for cross-reactivity between its digoxin antibody
7 and that drug?

7

8

A. No, I don't know that he did
8 that. I have no evidence to suggest with positive
9 confirmation that that was done.

9

10

Q. Thank you. Subsequent to 1974

11

have you been provided with any subsequent literature
12 from this manufacturer that alters in any way the
13 drugs identified either by adding to them or
14 eliminating them, to suggest that other tests for
15 cross-reactivity drugs had been made in respect of
16 the antibody for digoxin that they are providing,
17 or are we talking about the same list that applied
in 1974?

18

A. Yes, basically I have more
19 comprehensive list than that.

19

20

THE COMMISSIONER: Doctor, on

21

reading this could you not draw the conclusion that
22 they had tested for everything and that this was
23 what they had found?

23

24

THE WITNESS: Well, I think one can

25

K6



K7 1
2 conclude that the substances listed have been
3 tested for and found to be negligible. I don't
4 think the assumption can be made that other sub-
5 stances have been tested.

6 THE COMMISSIONER: Why would they
7 list - I don't understand what people would list
8 ones that are negligible and not list those that
9 weren't?

10 THE WITNESS: Right.

11 THE COMMISSIONER: Wouldn't that be
12 a little odd? What is the merit unless it is
13 comprehensive?

14 THE WITNESS: These substances are
15 found in blood serum, they are naturally occurring
16 substances.

17 THE COMMISSIONER: Oh, I see.

18 THE WITNESS: They are steroid
19 substances that might perhaps be considered to
20 cross-react with digoxin.

21 THE COMMISSIONER: Yes.

22 THE WITNESS: Because they are not
23 terrible similar to digoxin, even though they have
24 a similar kind of basic structure, the cross-reaction
25 is extremely low. I am a little surprised that they
didn't provide information on other digoxin derivatives.



K8

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25

I know that they did test other derivatives.
Prior to the preliminary hearing in December, 1981
I did contact the people down at Antibodies
Incorporated simply to obtain such a list of
extensive cross-reaction studies and so on.
Basically, they advised me that this material has
been available for such a length of time that their
records are incomplete with respect to this
particular sample.
The quality control manager indicated
to me that this particular material has been
available since about 1974. The Food and Drug
Administration in the United States required them
as a company to retain all this information after
about 1977 and so he was unable to supply me with
the detailed information that counsel is seeking.



1
2 He did write me a letter which
3 indicates the antiserum was produced by the method of
4 Smith, Butler and Haber and is highly specific for
5 digoxin and the cross-reaction with digitoxin is less
6 than 2 percent of the 50 percent inhibition level. I
7 think this single item indicates that this is really
8 a very highly specific antiserum, it obviously doesn't
9 exclude all the other substances that you have
10 mentioned, but many of the antisera that are
11 produced have very much greater cross-reaction for
12 digitoxin than this 2 percent level. The similarity
13 between digoxin and digitoxin is simply hydroxyl group
14 in one position.

15 Q. Dr. Ellis, so that I understand.
16 Other than the results with respect to digitoxin
17 reported to you in that letter from the Quality Control
18 Manager of Antibodies Inc., did he provide you any
19 information with respect to any other potentially cross-
20 reactant drugs which might react with this antibody
21 other than the ones you already knew about from the
22 brochure in 1974?

23 A. Right. He indicated to me a
24 reference in 1969 that related to the method of
25 preparation of the antiserum that he had actually used,
and so there is detailed information available on that



Ellis, dr.ex.
(Cronk)

1

2

particular method in 1969. In addition to that, cross-reference is made to a second paper where the whole issue of specificity of digoxin antibodies is brought up and I have copies of those which are available if you would like those.

6

7

8

9

10

Q. Thank you, Dr. Ellis. Let me just make sure again I understand this. I understand from what you are saying that the quality control manager referred you specifically first to information related to digitoxin and its cross-reactivity?

11

A. That is correct.

12

13

14

15

Q. Secondly, he referred you to an initial study that had been done in 1969 prior to the hospital using this particular antibody, and prior to your obtaining the 1974 brochure with respect to the cross-reactive drugs?

16

A. That is correct.

17

18

19

20

Q. In the 1969 literature reference provided to you is there any indication as to any other drugs which might be cross-reactive with this antibody, other than the ones set out in 1974?

21

22

23

24

25

A. I should point out that rabbits are individuals and you can inject the same compound into different rabbits and obtain an antiserum which has different qualities. Okay. So that you will get



1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25

2.3

a family of antiserums which may have similar, or may have different properties. So in the 1969 paper a different rabbit would have been used than the one referred to by this author, okay. Do you still wish me to give that information?

Q. Well if there is an easier way to do it Dr. Ellis, that is fine. Perhaps I can ask you this question. Insofar as you are aware today, are there any other drugs other than the ones disclosed in the 1974 materials, in respect of which Antibodies Inc. has done specific tests for cross-reactivity with the antibody that you are using in your RIA assay for digoxin?

A. It was my understanding from the Quality Control Manager that extensive studies had been done prior to introduction of this antiserum in 1974. Prior to that time extensive studies have been done. In fact, this antiserum has not only been sold to us it has been sold to Toronto General who used it for quite a number of years. It is my understanding it has also been supplied to independent companies in the United States.

Q. And as I understand it from what you said earlier because of the change in the requirements by the FDA, the identification of the drugs in



1

K2.4

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

respect of which those studies were conducted prior to 1974 were not supplied to you because they couldn't be by the Quality Control Manager of Antibodies Inc., is that correct?

A. That is the information he supplied me with.

Q. Thank you. Dr. Ellis, there is one other area, one further area that briefly I would like to deal with and that is, we have heard evidence from a number of witnesses concerning the particular property of digoxin and its inter-reaction with the body whereby digoxin by-products from metabolites can be created upon administration or introduction of digoxin to the body. Was that a factor of which you were aware in the period July 1980 to March '81 when you were running your RIA assays for digoxin?

A. You mean digoxin can be broken down in the body to other substances?

Q. Yes.

A. That potentially may resemble digoxin and potentially may cross-react in the radio-immunoassay, is that the question?

Q. That is right, were you aware of that? I am talking now about digoxin metabolites.

A. Yes. In general terms I was



K2.5

1

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

aware of this, in that most substances that are given to individuals are broken down in some way, or they may be excreted largely and altered, which I think is the case with digoxin.

Q. And as I understand it, Dr. Ellis, and perhaps you can tell me if this is a fair comment, some of the metabolites that are capable of being created by the body on the introduction of digoxin, some may or may not react in a way similar to digoxin in terms of the antibody that is used in the assay?

A. That is correct. Some of the derivatives are altered in such a way that they bind very poorly to some antibodies. In contrast, other antibodies the cross-reaction of those substances may be much more significant.

Q. Now in addition to digoxin metabolites or by-products that may or may not be produced by the body on introduction of digoxin, were you aware, again during the time frame of July 1980 to March 1981, in that time frame, were you aware of any other substance other than digoxin itself and digoxin metabolites which might react to the antibodies in the assay that you were running in a way similar to digoxin?

- - - -



L-1

1

2

3

A. I was not aware of those substances at that particular time.

4

5

6

7

Q. I take it because of the evidence that we have heard and the state of the literature today that you subsequently became aware of that school of thought and that research?

8

9

A. Of the digoxin-like substances or the compound X?

10

11

12

13

14

15

16

Q. Yes.

A. Yes. I think this kind of

ties in with several ideas. I could not understand, when I first came to the Hospital for Sick Children why, when we reported a result of 3 or 3.5 on an infant, on a very small child, to our neonatal nursery, why people were not a little bit more concerned than they were.

17

18

19

20

21

22

23

24

25

Basically on a number of occasions, for my educational purposes, when I first came to the hospital I would go up to the neonatal nursery and I would say, are you aware of this result and can you tell me what you are feeling about this result and so on. Basically they advised me at that particular time that they were very closely monitoring the clinical condition of the patient and the heart function of the patient and they were more



L-2

1

2

concerned about how that was behaving than
exactly what number we produced.

3

4

5

6

7

8

9

So that is the first piece of
information that perhaps in retrospect suggests
that not only are we measuring digoxin but perhaps
something in addition to this that cross-reacts
in our assay and may result in an apparently toxic
value when in fact the child is not showing any
symptoms of toxicity, okay.

10

Q. Yes.

11

12

13

14

15

16

A. The complexity of this is that
the response of the heart to a particular level
of drug is not constant throughout all the age
range, so it is quite -- it may well be quite
different in very small children anyway for other
reasons.

17

18

19

20

21

22

23

24

25

Q. All right, Dr. Ellis, again
talking the same time frame, July 1980 to March
1981, as I understand it there were in your mind a
couple of known factors in terms of the assays that
you were running. First, it was intended to encourage
the reactivity of digoxin to the antibody that you
were using so you expected the digoxin would cause
some reaction of interact with the antibody, pure
digoxin?



L-3

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25

A. Yes.

Q. Secondly, as I understand your evidence, you were aware that digoxin byproducts or metabolites might be produced which were of the kind which would react similarly, like digoxin, to the antibody?

A. But we would have no way of telling whether the result that we produced was entirely digoxin or five per cent of byproducts of digoxin at that particular stage or even now.

Q. That is my point, Dr. Ellis. The third known category of element at that time insofar as you are aware that could react to your antibody were the drugs described by the supplier of the antibody and you had information available to you from that supplier as to the likely degree of cross-reactivity you might suspect from those listed drugs. Is that correct?

A. Yes.

Q. Other than those three items you have told me that you were not then aware of what has been called in this courtroom substance X or the possibility of the existence of substance X. Correct?

A. Yes.



L-4.

1

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

Q. Now, for the purposes of the therapeutic monitoring of drugs that you are conducting, and specifically digoxin, during the period of July 1980 to March of 1981, if you could not tell from the assay results whether you were measuring pure digoxin, digoxin plus some mixture of digoxin metabolite reaction or digoxin plus a mixture of a drug that reacted similarly to digoxin, can you help me with how it could be said that a particular dosage of digoxin prescribed to a patient should or should not be altered, if you did not know in those terms what in fact was coming off your reading at the end of the assay.

A. Simply because I believe that the majority of the reading that we produce is digoxin. It relates to digoxin that was administered to the patient, in relation particularly to children over six months of age. I think I have to qualify that in relation to yesterday's testimony.

Q. That was your belief at the time?

A. Very much so, yes.

Q. Can you tell me on what --

A. There is a fourth qualifier. You gave me three, I think, a list of three reasons --



L-5

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25

three possible reasons why I would have reason to believe that what I was measuring was digoxin. I think there is fourth one.

Q. All right.

A. And the fourth one is over a long period of time, since probably 1975 right to the present time, this test has been used with all types of patients in the hospital, lots of them. Lots of blood samples have been taken. Many of those patients have been treated with drugs such as furosimide that you mentioned. To my knowledge no one has come along and said, look, here is a child who we did not treat with digoxin but we did treat with furosimide and you produced a digoxin level for us. So I think we have some kind of, admittedly a little bit tenuous, indication that for clinical purposes furosimide and all the other drugs used in the hospital don't have a major significant effect on the result that we produce. I think that is shown in the literature as well. If you really look at the cross-reaction of furosimide and these other drugs that people have brought up, they are really quite low in many instances.

Q. Dr. Ellis, would it be fair to say that, again dealing with the July 1980 to March



I-6

1

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

1981 time frame that when an assay result for digoxin was obtained, recognizing that as you then understood it there were three possible components to why that level was being obtained, digoxin itself, digoxin metabolites and drugs that had an affinity for the antibody in a fashion similar to digoxin itself, that you could not discount for therapeutic reasons the fact that that level might be a pure digoxin level. You could not eliminate that, for obvious reasons, as a possibility.

A. I could not eliminate what?

Q. You could eliminate the possibility that what you were in fact getting was a pure digoxin reading.

THE COMMISSIONER: I think there is something wrong with the negatives there, somewhere. You could not be assured that what you were getting was a pure --

MS. CRONK: Q. As I understood what you said, Dr. Ellis, you were content at the time for the reasons that you have outlined that what you were in fact getting a reading on, during that time period, was pure digoxin. Is that correct?

A. Yes, I suppose so.

Q. I would like you to be sure



L-7

1

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

about that. As I understood what you said, for your purposes in running those tests when you got a test result on a digoxin assay, you considered that to be a level indicative of digoxin in the sample on which you had run the assay. Is that right?

A. Yes, we would report the digoxin equals which implies that we believe that we were measuring digoxin, just as everyone else believed they were measuring digoxin, except in very exceptional circumstances and other interferences of a very complex nature that radioimmunoassays are susceptible to.

Q. You knew that of those possibilities part of what you were measuring could in fact be the result of the action of digoxin metabolites or drugs that had an affinity or an avidity for the antibody, similar to digoxin itself. You knew that?

A. Yes, but I believe those to be very small.

MS. CRONK: Thank you.

Mr. Commissioner, I do not have any further questions of this witness. I do not know what your intentions are with respect to the



L-8

1

2

afternoon's session, sir.

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

THE COMMISSIONER: I am not

absolutely sure yet either. I think we have come
to June the 30th and, strangely enough, the inquiry
is not yet complete. I think as we are going on
during this summer I doubt if there will be too
many vast editorials if we do not proceed this
afternoon.

However, I am thinking of you, Mr.
Roland, if you wanted to ask some questions before
we adjourned --

MR. ROLAND: Of this witness?

THE COMMISSIONER: Yes.

MR. ROLAND: No, I have no questions
as this time of this witness. I would like to be
put in the position of asking my questions of
Dr. Ellis last.

THE COMMISSIONER: I think that is
a legitimate request, and it will be granted without
consulting anybody else.

I think, unless you are all going
to be furious, I think we will postpone the cross-
examination until -- you are available on Tuesday,
are you, Doctor?

THE WITNESS: Yes.



L-9

1

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

THE COMMISSIONER: It may spoil your holiday, but it might spoil it worse if we proceeded with it now.

THE WITNESS: Okay.

THE COMMISSIONER: We will rise now. Is there anything else, Miss Cronk?

MS. CRONK: No, Mr. Commissioner. We will recall Dr. Ellis for cross-examination on Tuesday.

THE COMMISSIONER: I understand that some doctor is being interviewed and one of counsel has to be present while he is being interviewed, so that is another excuse for not proceeding this afternoon, so until Tuesday at 10:00 o'clock.

MS. CRONK: Thank you, Mr. Commissioner. Thank you, Dr. Ellis.

---Whereupon the hearing adjourned at 1:00 p.m. until Tuesday, July 5th, 1983 at 10:00 a.m.

